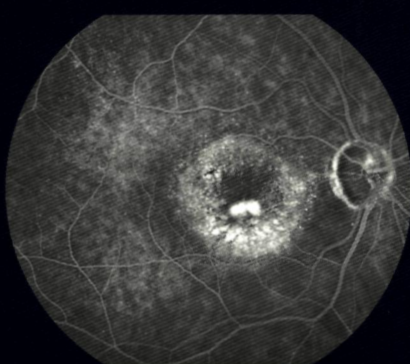
RADIOTHERAPY FOR SUBFOVEAL CHOROIDAL NEOVASCULARISATION IN AGE-RELATED MACULAR DEGENERATION



G.J. BERGINK

RADIOTHERAPY FOR SUBFOVEAL CHOROIDAL NEOVASCULARISATION IN AGE-RELATED MACULAR DEGENERATION

A clinical study in patients with age-related subfoveal neovascular macular degeneration

Cover illustration: Top, *subfoveal age-related choroidal neovascularisation of a right eye (color).* **Bottom,** *fluorescein angiogram of the same eye.*

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RADIOTHERAPY FOR SUBFOVEAL CHOROIDAL NEOVASCULARISATION IN AGE-RELATED MACULAR DEGENERATION

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De één kan het niet doen en de ander kan het niet laten.

(F. Swarttouw)

Aan mijn vader
Voor Saskia en Gijs

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Contents

ABBREVIATIONS

AMD	Age-related Macular Degeneration
ARM	Age-related Maculopathy
CNV	Choroidal Neovascularisation
DA	Disc Area
FA	Fluorescein Angiography
FAZ	Foveal Avascular Zone
Gy	Gray (dose of irradiation)
ICG	Indocyanine Green
MPS	Macular Photocoagulation Study
PED	Pigment Epithelial Detachment
RPE	Retinal Pigment Epithelium
VA	Visual Acuity
SS	Scar Size

CHAPTER 1

INTRODUCTION

1.1. GENERAL INTRODUCTION

Age-related maculopathy (ARM), formerly known as senile macular degeneration, is the leading cause of irreversible severe loss of central vision in developed countries including the U S A and Europe [1] ARM is a clinical diagnosis and represents a broad spectrum of diseases of progressive aging and degenerative changes in the human macula, including drusen and hyper- or hypopigmentation of the retinal pigment epithelium (RPE) ARM occurs in 20 % of individuals over 65 years of age and the prevalence increases to 35 % in subjects older than 74 years [1] As older adults become a larger part of our future population, the significance of ARM as a public health problem will increase

The late stages of ARM are called age-related macular degeneration (AMD) and can be subdivided into a "dry ' or atrophic form leading to geographic atrophy, and a "wet" or exudative form representing choroidal neovascularisation (CNV) in the macular area The prevalence of exudative AMD is about 1-2 % in people older than 55 years, and increases with age as well [1]

Patients presenting with drusen and pigment changes can lose central vision by two different mechanisms They can develop progressive geographic atrophy of the RPE, unassociated with exudation or hemorrhage, with progressive visual loss over years and the occurrence of a central scotoma This "dry" or atrophic type of AMD occurs in 80-90 % of patients, but accounts for only 5 10 % of severe central visual loss defined by a visual acuity (VA) of less than 0 1 The exudative stage can develop when new choroidal vessels penetrate Bruch's membrane, resulting in CNV, with leakage of fluid and blood under the RPE and the neuroretina in the macular area

Symptoms of CNV in the foveal area are significant loss of central vision, metamorphopsia and reduced color vision Although only 10-20 % of patients with AMD have the exudative form of the disease, it accounts for 80 90 % of patients ending up with a VA less than 0 1 [1,2] The chance that the fellow eye will develop CNV as well increases with 5-10 % each year If this happens, the patient becomes legally blind Patients with the exudative stage of AMD in both eyes will not lose total vision, but with a VA of less than 0 1, they do have lost the possibility of reading, recognizing people and performing daily routine life activities The deterioration of the VA in case of a subfoveal CNV often happens rapidly, in weeks to months, but sometimes takes a slower course over more than three months to one year Knowing that the visual prognosis for AMD patients presenting with subfoveal CNV is poor, many attempts have been made to inhibit or stop the growth of the CNV in order to maintain central vision

Current knowledge concerning the natural course and laser therapy options for subfoveal CNV has recently been provided by the macular photocoagulation study (MPS) group [3] Laser therapy causes local damage to the retina and results in impairment of central vision, especially when a subfoveal lesion is treated In order to benefit from a smaller central scotoma after 18 months post-treatment, patients have to accept an immediate and definite loss of VA [3] However, recurrences of CNV in eyes after initially well performed laser treatment occur in at least 50% Therefore the majority of patients with the exudative form of subfoveal AMD can not be offered any effective therapy at all The aim of any treatment of CNV should not only be to prevent visual loss but also to keep the associated central scotoma as small as possible Low vision aids provide some help and always prove more helpful when the scotoma is small

In the past, some experience with radiation treatment of neovascular age-related disease has been obtained, but it was never thoroughly investigated nor documented In 1990 the departments of Ophthalmology and Radiotherapy of the University Hospital Nijmegen were the first to design a pilot study on the effect of radiation therapy for subfoveal CNV, with the aim to find the optimum dose which would stop the proliferation of CNV membranes, without exceeding the tolerance levels of the ocular structures At that time, the idea existed that a relatively high radiation dose applied to the macular area would stop the process of CNV and would obliterate aberrant newly formed vessels

1.2. AIM OF THE STUDY

The objective of this study is to determine whether radiation therapy alters the natural course of age-related subfoveal CNV membranes, either by maintaining a stable VA and stable central scar size (SS) or by decelerating the decrease in VA

The next chapters present respectively a review of the disease AMD (Chapter 2) and of the principles of radiotherapy (Chapter 3) A pilot study was conducted to find a dose-effect relation and to study the efficacy of radiotherapy for neovascular AMD The subsequent chapters present the results of this pilot study concerning radiation therapy for age-related subfoveal CNV, compared with natural history data These have been published before and are reprinted from the journals (Chapter 4,5,6) A randomized clinical trial, based on the results of the pilot study, was started in order to evaluate this therapy The results of a the randomized trial with an untreated control group are described in Chapter 7 Finally, Chapter 8 discusses the conclusions and future perspectives concerning this experimental therapy

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CHAPTER 2

AGE-RELATED MACULAR DEGENERATION (AMD)

2.1 HISTORY OF AMD

History

As was indicated in the introduction, in Europe and the U S A visual loss due to macular degeneration is a substantial problem because it occurs in about 20 % of the population over 55 years of age [1,2,3] Many research groups have been working on the pathophysiology, the diagnostic and therapeutic options of this disease [1,2,3,4,5,6] The number of patients with AMD in both eyes is growing and they can be considered to be legally blind [7] During the last two decades the MPS group provided information concerning the natural course and efficacy of laser treatment in patients with exudative CNV lesions in AMD [8-18]

Age-related macular degeneration was first described in 1875 by Pachenstecher and Genth in the "Atlas der pathologischen Anatomie des augapfels" [19] They described a disc shaped macular lesion However, it was Oeller who in 1905 introduced the term "disciform degeneration of the macula" [20] The term "senile macular degeneration" has been used, since it was first described as a clinical entity by Haab in 1885, to refer to a variety of pigmentary and atrophic changes in the macular region [21]

In 1926 Junius and Kuhnt published a book "Die scheibenformige Entartung der Netzhautmitte (degeneratio maculae luteae disciformis)" concerning ten elderly patients with disciform subretinal lesions, now known as the end stage of exudative macular degeneration [22] They compared their observations with the "retinitis circinata" cases described by Fuchs in 1893 [23] Although they recognized the influence of vessel leakage on the pathogenesis, the subretinal origin of the disease was unknown They concluded "Degenerative Veranderungen in der Netzhaut als Folge von Gefaßkrankheit im makularen Ernahrungsbezirk, welche in verschieden langen Zeitraumen ablaufen und im Wesentlichen auf den zentralen Netzhautbezirk innerhalb der temporalen Gefaßbogen beschrankt bleiben, sind neben progressiven Gewebsbildungen variabeler Art der "retinitis circinata" und der "scheibenformigen Erkrankungen der Netzhautmitte" gemeinsam"

In 1967 Gass first described in a historic monograph, "Pathogenesis of disciform detachment of the neuroepithelium", the hypothesis of the development of choroidal neovascularisation (CNV) occurring in the macular area because of age-related changes in the retinal pigment epithelium (RPE) and Bruch's membrane related to drusen [24] Gass postulated "Senile macular degeneration is characterized by mottling of the RPE, drusen formation and loss of the foveal reflex Primarily degenerative changes in the choriocapillaris and Bruch's membrane are considered with secondary alterations in the RPE and retina Defects in Bruch's membrane and neovascular invasion of the sub RPE space from the choroid represent complications of senile macular degeneration, which predispose the eye to the development of serous and hemorrhagic disciform detachment and degeneration of the RPE and retina" However, in 1959, Maumenee had been the first who assumed that the blood between the RPE and Bruch's membrane derived from the choriocapillaris [25] During the end of the sixties and the beginning of the seventies the first results of photocoagulation therapy in early senile macular degeneration became available [26,27] Since 1982 until recently, the MPS group provided information concerning the natural course of CNV in AMD and data of laser photocoagulation treatment applied in these cases [8 18] During the last two decades many ophthalmologists obtained experience with laser treatment, to which we will return below [26,27]

2.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence

As was mentioned before, the late stages of ARM are characterized by geographic atrophy and neovascular disease, which is also called AMD, and are important causes of severe visual impairment in the eldery in industrialized countries [1,2,3] Whatever definition or method of diagnosis, all estimates show a strong rise with age, and a reasonable overall prevalence for any type of ARM in the age-groups 65-74 years and 75-84 years is 20 and 35 percent, respectively [29]

The Framingham Eye Study (USA) noted the presence of AMD in one or both eyes in 5 7 % of persons older than 52 years [3] Drusen were noted in approximately 25 % of all persons but only 5 7 % had drusen with a decrease in VA (< 20/30), defined as AMD The Beaver Dam Eye Study (Wisconsin) assessed the prevalence of the features of AMD [1] The prevalence of any AMD, including drusen, RPE atrophy and/or hyperpigmentation or exudative disease, was 19 4 % in subjects between 65 - 75 years and 36 8 % in those older than 74 years

The Rotterdam Study was the first major European study providing population-based data on AMD [29] Comparison with other population-based studies, concerning atrophic and neovascular AMD, was done with the Chesapeake Bay Study and the Beaver Dam Eye Study in the United States [30,1]. In the Rotterdam study the prevalence of neovascular AMD increases from 0.1 % in subjects of 55 to 64 years of age to 7.4 % in persons of 85 years or older [29]. The prevalence of atrophic or neovascular AMD in the total population was 1.7 %, but 11 % in the population older than 85 years and 3 7 % in the age group of 65 - 75 years. In the Beaver Dam Study the prevalence of AMD in the age group of 65 - 75 years was 7.1 % [1] Hence, comparison between the Rotterdam study, the Chesapeake Bay study and the Beaver Dam Eye Study indicates that AMD might be less common in the European population.

A prospective ophthalmic survey of a population in the USA revealed that of people aged 45 years or more, 1.2 % have active CNV disease [31]. Recently observations have been published that show that in Britain the incidence of visual loss caused by AMD has increased in the past 50 years [32]. However, changes in diagnosis and detection of this disease could also be an explanation for this hypothesis.

Risk factors

In the population-based studies many risk factors for the development of AMD have been studied [3,29,30]. Familial occurrence of AMD has been observed, expecting a genetic component to be involved [33,34,35]. A prospective ophthalmological study of 50 spouses and 53 sibling pairs showed a trend towards concordance of drusen characteristics between siblings and not between spouses [33]. These results support the view that genetic factors play a role in the pathogenesis of ARM.

Beside age, no definite risk factor has been isolated, however conflicting results have been found concerning the association between AMD and cardiovascular disease, AMD and UV-light exposure and AMD and antioxidant status [36,37,38]. Basic research revealed evidence for a possible protective effect of antioxidant nutrients like zinc, selenium, vitamine A and vitamine C [39,40,41,42] The retina and choroid contain high concentrations of zinc and selenium necessary as a cofactor for metalloenzyme systems. These systems are involved in the defense against the oxidative threat of the free radical species that are generated by light in the retina In general, antioxidant vitamins and zinc have a protective effect on light-induced oxidative photoreceptor damage and studies in experimental animals have stimulated interest in the relationship of these micronutrients and AMD The Eye Disease-Control Study Group suggested a protective effect against neovascular AMD of higher serum anti oxidant levels of vitamine C and E, selenium and carotenoids (lutein, zeaxanthin) However at present no decided recommendations can be made for taking micronutrient dietary supplementation [31] In a study by Vinding et al age, smoking and the daily use of hypnotics (sedative drugs) proved to be significantly associated with AMD [38]

The Rotterdam Study, the Beaver Dam Study and the Chesapeake study all found an association between AMD and age and AMD and smoking [29,1,30] Besides, the Rotterdam Study provided information concerning the association between AMD and atherosclerosis, AMD and women with an early menopause and AMD and smoking [43,44,45] Particularly a relation between smoking and the neovascular form of AMD was observed current smokers younger than 85 years had a 6 6-fold increased risk of neovascular AMD compared to those who had never smoked [44]

Altogether, the concept of genetic predisposition influenced by environmental factors, including diet and smoking, in eldery people is reasonable [46,47,48,49,50] Currently, there is no convincing evidence that nutritional supplementation can affect the development or progression of AMD, however smoking is a major risk factor and issue to prevention

2.3 MACULAR ANATOMY

The sensory retina (from the photoreceptor cells to the inner limiting membrane) varies in thickness from 0 5 mm in the fovea to 0 2 mm at the equator It is a delicate transparent tissue, in the macular area supplied by the superior and inferior branches of the central retinal artery In approximately 20 % of the patients a cilioretinal artery supplies the papillo-macular area When the RPE is intact, it blocks small molecules, like fluorescein, to enter the subretinal space from the choriocapillaris This is called the outer blood-retinal barrier The inner blood-retinal barrier is composed of the retinal vascular endothelium The retina receives a dual blood supply, one from the choroid, which supplies the RPE and the photoreceptors, the other from the retinal vessels, which supply the inner retinal layers In a normal macula the choriocapillaris supplies the RPE cells and photoreceptors and the outer part of the retina up to the outer plexiform layer of nutrients The peculiar structure of the choroidal vascular tree in the macula provides this area with the highest rate of blood flow of any tissue in the body [5] The specialized structure in the macular region accounts for the predilection of certain disease processes to involve this area and for the variety of ophthalmoscopic changes [5]

Histologically, the macula is defined as that portion of the retina that contains two ore more layers of ganglion cells, with a high concentration of cones and a thick inner limiting membrane Anatomically the macula (macula lutea or central retina) is defined as that portion of the posterior retina that contains xanthophyllic pigment and two or more layers of ganglion cells The center of the normal macula lutea, the yellow spot, is the fovea (Figure 1)

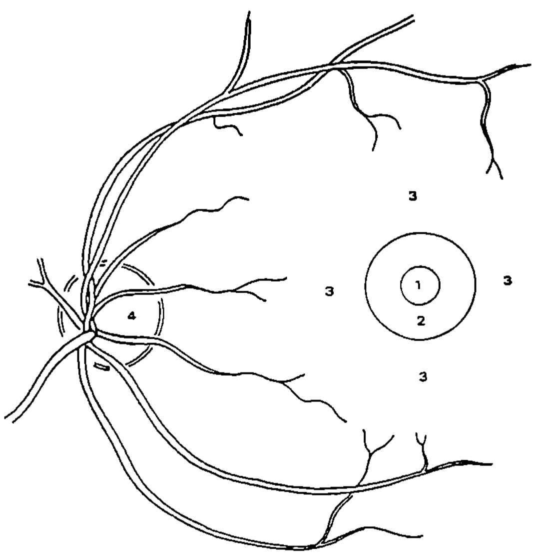


Figure 1. *Posterior pole*

1 The foveola with (diameter 0 35 mm) and the foveal avascular zone (FAZ, diameter 0 5 mm) 2 The fovea (1 5 mm diameter) 3 The posterior pole, macular area (5 mm diameter) 4 The optic disc (1 5 mm diameter)

The fovea with a diameter of 1 5 mm has a central part, the foveola, consisting of only cone photoreceptors This area has no capillary bloodvessels and is known as the foveal avascular zone (FAZ) However, the anatomic subdivisions of the macula are ill defined ophthalmoscopically The center of the macula usually appears as a poorly defined zone of slightly greater pigmentation than its maximum in the foveolar area

The macular area is the location of central visual function, emphasized by the fact that one third of the nerve fibers of the optic disc originates in this area The photoreceptors are highly specialized cells that absorb light Cones are responsible for what we consider to be normal vision, that is, fine central vision and color vision This is reflected in the great number of second- and third-order neurons subserving the cones The photoreceptors depend upon the RPE for nourishment and maintenance The RPE is a monolayer of pigmented cells located between the neuroretina and Bruch's membrane and is more highly pigmented in the central macular area than elsewhere The degree of pigmentation of the RPE and the choroid varies according to the pigmentary characteristics of the individual In the RPE cytoplasma lipofuscin granules are found, which are residual bodies, representing the end product of phagosomal activity Incomplete digestion of shedded discs ends up with vesicles with debris called lipofuscin granules [5] Bruch's membrane consists of the basement membrane of the RPE on the inside and the basement membrane of the choriocapillaris on the outside and lies between the basal laminae of the RPE and choriocapillaris endothelial cells

In summary, the function of RPE cells consists of phagocytosis of the outer segment discs, pumping fluid from the sub-retinal space to the choriocapillaris, keeping the neuroretina attached, absorbing the light which has passed the photoreceptors and scavenging the free radicals formed by the light energy and the high oxygen flux in the macular area [2,5]

2.4 PATHOPHYSIOLOGY

Introduction

In patients with ARM and AMD, changes have occurred in the retina, the RPE and the choriocapillaris [48,49,50,51,52,53] Prominent signs are the development of drusen and the hypo- and hyperpigmentation of the RPE in the macular region As was indicated, visual loss in AMD patients results from subretinal neovascularisation and detachment of the RPE in the exudative stage and from drusen and geographic atrophy in the dry stage

In older individuals, Bruch's membrane is thickened due to accumulation of cellular debris caused by degeneration of the RPE [52,53] The accumulation of debris, derived from the RPE, in Bruch's membrane is a progressive phenomenon with age, and is seen consistently by the age of 60 years Multinucleated giant cells appear to participate in the breakdown of Bruch's membrane and, together with diffuse disease of the RPE and changes in the physicochemical properties of Bruch's membrane, may provide angiogenic stimuli for CNV [51,52] The progressive changes in Bruch's membrane are believed to be responsible for the various events It is known that the RPE moves fluid outwards from the subretinal space in the direction of the choroid and that the conductivity of Bruch's membrane declines with age leading to detachment of the RPE When the RPE and subsequently the neuroretina becomes separated from Bruch's membrane, functional loss starts with photoreceptor atrophy Loss of photoreceptors in the outer neuroretina is a constant association with age [48] Below the role of lipofuscin, drusen, the choriocapillaris and neovascular changes in the development of AMD will be discussed

Lipofuscin

Lipofuscin granules are lipid/protein aggregates which are considered to be the life long accumulation of lysosomal residual bodies, the end products of photoreceptor degeneration [51] With increasing age, as a result of oxidative damage to the photoreceptor membrane, human RPE cells accumulate lysosomal lipofuscin, and this may be associated with impairment of RPE cell function Lipofuscin deposits are also found in Bruch's membrane, possibly associated with the pathogenesis of AMD However no correlation has been found between the amount of lipofuscin and the development of AMD Accumulation of lipofuscin granules in the RPE is not associated with deposition of lipoidal material in Bruch's membrane Both processes may represent independent age-related phenomena [51,52,53]

Drusen

The presence of drusen, at the level of Bruch's membrane, is considered to be the primary indicator of age-related changes [54,55,56,57] Drusen in the macular area were first described by Donders in 1855 [58]. The clinical classification of drusen distinguishes between hard, soft and basal laminar drusen [57,59,60].

Hard drusen are small yellow-white deposits with a well-demarcated border (Figure 2). The RPE cells on top of the hard drusen are hypopigmented. Small hard drusen appear in 6.2 % of all eyes with ARM and do not seem to predispose to CNV. Soft drusen on the other hand appear on ophthalmoscopy as yellow-white spots with indistinct (soft) borders and tend to become confluent leading to separation of the RPE from Bruch's membrane [60,61]. The RPE on top of soft drusen is often atrophic Finally basal laminar drusen should be regarded as focal thickenings of the RPE basement membrane rather than deposition of material between this membrane and the inner collagenous layer of Bruch's membrane. Dissappearance of drusen has also been recognized and may be related to macrophages or multinucleated giant cells [57]. Basal laminar deposits and basal linear deposits have histologically been described as extracellular deposits between the RPE and its basement membrane. The pathogenesis is unknown and their role in the development of AMD is uncertain [62,63]. In a study of 126 patients with bilateral drusen cumulative incidence of new drusen lesions proved to be 8.55 % at 1 year, 16.37 % at 2 years and 23,52 % at 3 years [57].

The appearance of drusen on fluorescein angiography (FA) gives information about their nature and prognosis [5] Large confluent drusen which are hypofluorescent on FA have a predisposition towards pigment epithelial detachments (PED) rather than CNV [48,49,50]. These lipid riche deposits are hydrophobic and reduce the conductivity of Bruch's membrane, leading to accumulation of fluid in the sub-RPE space. The decline in the hydraulic conductivity of the Bruch's membrane-choroid complex with age implies a decreased capacity for the exchange of fluid between the choroidal and retinal pigment epithelial compartments. Hydrophylic drusen are hyperfluorescent on FA, and are at risk for developing CNV [48,49,50] Fluorescence may be dependent on the quantity of pigment in the overlying RPE, or more importantly, on the presence or absence of fluorescein within drusen material. Frequently, more hard drusen will be visible on FA than by ophthalmoscopy.

Choroidal changes

It is uncertain whether changes in the choriocapillaris are secundary to other changes in the macula or whether they in fact are the initiating factors of AMD.

There is evidence that the flow of blood in the choroid of AMD affected eyes is impaired, but so far neither the nature nor the cause of this impairment has been established [64] A combination of increased pulsatility and decreased velocity of the short posterior ciliary arteries is observed in AMD, and can probably be interpreted as evidence of increased vascular resistance Impaired choroidal perfusion results in degradation of the metabolic transport function of the RPE [64] One study suggested that in the dry stages of AMD blood flow is reduced, whereas in the exudative stage the ocular blood flow is in the same range as in the matched control group [65] However clinical and experimental evidence shows that RPE dysfunction in most cases leads to secondary atrophy of the choriocapillaris

Neovascularisation

CNV vessels originate from the choriocapillaris and penetrate Bruch's membrane either by pre-existing or by newly formed breaks (Figure 2) The new vessels leak serous fluid, proteins, lipids and blood under the RPE, eventually leading to RPE detachment When the sub-RPE fluid breaks through the RPE, a neurosensory retinal detachment occurs When the subretinal hemorrhage becomes invaded with fibroblasts, a fibrovascular disciform scar is formed In the development of CNV, not only the amount and composition of drusen is important, but also the concentration of various growth factors derived from the RPE and the presence of macrophages in Bruch's membrane It might be that activated macrophages induce the vasoproliferation by the production of growth factors [66,67,68,69,70] On the contrary there is also a possibility that RPE cells sometimes release an inhibitor of neovascularisation [71] Finally hypoxia has been assumed to be a factor in the pathogenesis of ARM and subsequently of exudative AMD [69]

Histopathologically the initiation of CNV is often associated with the presence of a basal laminar deposit, basal linear deposit and soft drusen Large soft drusen and focal hyperpigmentation are associated with an increased risk for the for the development of CNV [68,69] Ultrastructural features of classic CNV include a central core of subfoveal CNV surrounded by a peripheral rim composed of fibrin, photoreceptor outer segments and macrophages often accompanied by a low-grade chronic inflammatory reaction [72,73,74,75]

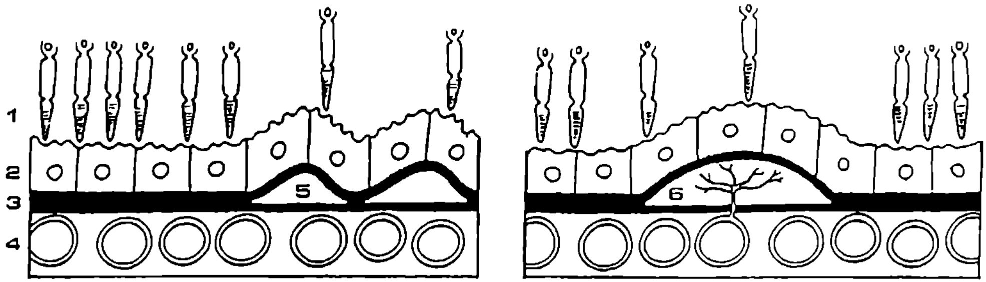


Figure 2: *Localisation of drusen (left) and subretinal choroidal neovascularisation (CNV, right) 1 photoreceptor cells 2 RPE cells 3 RPE basement membrane and Bruch's membrane 4 Choriocapillaris 5 Drusen 6 CNV located sub-RPE*

Geographic atrophy

In the end stage of "dry" AMD, only choroidal vessels are visible on ophthalmoscopy because of the atrophic changes in the neuroretina, RPE and choriocapillaris Geographic atrophy is caused by the disappearance of RPE and associated photoreceptor cells occuring in the late stages of ARM When the fovea is involved, gradual spread of geographic atrophy leads to visual loss In a study by Schatz et al it was noticed that areas of atrophy occurred where drusen or pigment epithelial detachments had been located before [76] CNV cannot occur in a region of geographic atrophy because viable RPE-cells are necessary for the development of neovascularisation [76]

Conclusions

One of the first steps in the development of atrophic AMD is the accumulation of abnormal material in Bruch's membrane (drusen), very often leading to RPE detachment and programmed cell death (apoptosis) of RPE cells As a consequence, secundary atrophy of the choriocapillaris with increased vascular resistance develops, with subsequent cell death in the overlying retina [48,49,50,56] The symmetry of drusen in terms of quantity, distribution, and chemical composition together with the concept that the form of Bruch's membrane deposits determines the nature and magnitude of risk to vision, suggests that the two eyes of a patient should behave in a similar manner [50] Also certain genetic and environmental factors are part of the aetiology of the disease [48,50]

Concerning the neovascular stage (Figure 3), it has been proposed that diffuse disease of the RPE, changes in the chemical properties of Bruch's membrane, drusen and hypoxia of the outer retina may all be interrelated factors leading to a release of angiogenic stimuli [50] Although these are interesting hypotheses, the mechanism by which CNV in AMD affected eyes is induced is still not really understood

Age	→	Atherosclerosis	←	Environmental factors
Genetic factors		Cardiovascular disease		* Smoking
				* Antioxidant status zinc, selenium vitamine A,C,E carotenoids (lutein, zeaxanthin)
				* UV-light
				* Oxidative damage (free radicals)

↓

AMD

Bruch's membrane ↔ drusen
RPE ↔ lipofuscin
Choriocapillaris ↔ blood flow

↓

Breaks in Bruch's membrane
Hypoxia
Growth factors, VEGF, TGF-ß

↓

Neovascular AMD

Figure 3: *Multifactorial pathogenesis of neovascular AMD*

2.5 CLINICAL FEATURES AND DIAGNOSIS

Clinical features

The varied manifestations of AMD are subdivided in two categories

1 Non-neovascular AMD = Atrophic AMD = "dry" AMD

2 Neovascular AMD = Exudative AMD = "wet" AMD

Both are often considered separately, however it should be recognized that they are merely different clinical end points of a common pathophysiology [8-18,77] On the other hand, they have to be distinguished from one another because of the difference in visual prognosis

Atrophic AMD

The majority (80-90 %) of AMD patients develop geographic atrophy of the macula secondary to hypo- or hyperpigmentation of the RPE The disease usually presents with decreased central vision in one eye, although the disorder is always bilateral, the contralateral eye will often sooner or later experience similar visual impairment The majority of patients with "dry" AMD maintain a VA of at least 0 1 However it accounts for 5-10 % of legal blindness in AMD Geographic atrophy corresponds to well delineated areas of chorioretinal atrophy sometimes with an increased visibility of choroidal tissue Areas of atrophy appear as transmission or "window" defects on FA although staining of areas corresponding to geographic atrophy may occur Reading disability is the main complaint of patients with maculopathy Therefore the area of eccentric retinal fixation must be of sufficient size to allow reading ability by magnifying low vision aids [79,80] When the foveola becomes involved in the atrophic process, the patient must shift from central to eccentric fixation [80] Visual loss in geographic atrophy is nearly always perceived by the patient as a gradual process A possible explanation for this is a transitional period during which a patient uses both a foveal and a extrafoveal site for fixation The complaint of sudden loss of VA of a patient with geographic atrophy should always raise the suspicion of CNV [82,83]

Neovascular AMD

The exudative or "wet" stage will develop in 10-20 % of the patients, which means that CNV arising from the choriocapillaris penetrates Bruch's membrane and proliferates beneath the RPE layer and/or in the subretinal space Subfoveal CNV often leads to rapid loss of central vision within a period of weeks or months However, it is not possible to predict how fast the drop in VA occurs as this differs between individuals CNV appears clinically as a gray to green subretinal lesion often associated with the elevation of the overlying neurosensory retina The CNV vessels leak blood, lipid and fluid, which causes further visual impairment Only after an investigation including fluorescein photographs, the differentation between classic, occult and mixed type CNV can be made [82,83,84,85] The natural course is one of fibrotic regression and scarring, with atrophy of the overlying retina and underlying RPE Fibrous tissue develops into a "disciform scar", which indicates only that the scar is circular in form Functionally, this results in extensive central scotoma and a complete loss of central vision and color vision A fibrovascular disciform scar may vary in color from white to yellow to brown to black, depending upon the degree of RPE-hypertrophy, and is frequently associated with subretinal fluid, hemorrhage and lipid

Diagnosis

The differential diagnosis of CNV consists of CNV developing before the age of 50 years and age-related CNV in individuals older than 50 years Visual loss associated with CNV in patients younger than 50 years is uncommon and can be due to various causes The etiology of CNV in a study of younger patients (n=363) turned out to be high in myopia (62 %), idiopathic (17 %), histoplasmosis syndrome (12 %), and angioid streaks (5 %) [86]

When a patient, older than 55 years, enters the out-patient clinic with complaints of reduced VA with metamorphopsia and on ophthalmoscopy signs of AMD, further diagnostic procedures are needed, which will be discussed below Moreover in case of visible longstanding exudative disease it is important to ask the patient for photopsias and visual hallucinations In a study of 100 patients with exudative disease, 59 % had a history of seeing flashing light i e photopsias, and 12 % experienced formed visual hallucinations known as Charles Bonnet syndrome [87]

1. Visual acuity

In the MPS-group visual acuity (VA) is measured by use of Bailey-lovie charts A loss of 3 lines VA represents doubling, and a loss of 6 lines represents quadrupling of the minimum angle of resolution, eg, a change from 20/80 (0 25) to 20/160

(0 125) and 20/320 (0 0625) Snellen equivalent, respectively Best-corrected VA is tested using the Snellen chart Although this mode of testing is subjective and represents only a threshold object size about which the patient can make a correct judgment, the Snellen chart remains the universal standard of baseline VA because of its accuracy, reproducibility and ease of interpretation by both patient and clinician [79] The VA for distance, tested with the Snellen chart, is strongly associated with the ability to read titles from a large print [79] The Amsler-grid test for metamorphopsia usually follows the VA estimation In case of AMD, the patient will notice small scotomas and changes in straight lines

2. Fluorescein angiography

As will be clear fluorescein angiography (FA) is the most important diagnostic tool when patients present with clinical signs of AMD According to the MPS-group, for the last two decades FA has been the mainstay for evaluating the retinal and choroidal circulation in general and has proven to be the most important value for the diagnosis of CNV The normal FA clearly documents the dual nature of the retinal circulation It starts with the filling of the large choroidal vessels and choriocapillaris the background choroidal fluorescence, followed by that of the arteriolar filling phase The choriocapillaris vessels are close together and normally leak fluorescein resulting in the choroidal flush Fluorescein does not normally gain acces to the subsensory retinal space, because of the RPE tight junctions (the outer blood-retina barrier) The retinal capillary transit occurs while the extravascular space of the choroid is perfused with dye The retinal capillaries do not leak fluorescein normally (the inner blood-retina barrier) Because the two separate circulations normally do not overlap and there is avascular tissue i e the outer retina and the RPE between the two, the sensation of depth helps the viewer to define the level of pathologic processes [5]

Abnormalities in the FA can be understood as the presence of too much hyperfluorescence, or too little fluorescein hypofluorescence The presentation of possible CNV depends on the pattern of hyperfluorescence seen on the FA In the past only lesions described as "classic" type of CNV were classified properly Until the MPS criteria were developed many terms, like occult CNV and poorly demarcated CNV, were used synonymously, while not describing the same fluorescein pattern Various studies also noticed difficulties with the detection of recurrent CNV after laser photocoagulation were For example, recurrences of

CNV after laser treatment can be identified by focal staining and speckled hyperfluorescence along the edge of the laser lesion [80] And a comparison between clinical examination and FA in detecting recurrent CNV showed the identification of a recurrent CNV in 12 % of eyes (n=137) on the FA in which it was not suspected on clinical biomicroscopy [82] Pigment epithelial detachments (PED) with a focal hyperfluorescent spot were thought to be associated with a high risk of developing CNV, but are now classified according to the MPS-group as occult CNV [81] The MPS group presented an international classification of angiographic presentation of CNV which will be discussed below[8-18]

Definition of a classic CNV

Area of well-demarcated bright hyperfluorescence, often a net of vessels, throughout the early phase of the FA, with leakage in the mid and late phase frames Vessels of the CNV will be visualized in the early phase but are not required to be identified In later phases progressive pooling occurs, which usually obscures the boundaries of the CNV (Figure 4)

Definition of occult CNV

Type I Fibrovascular pigment epithelial detachment·

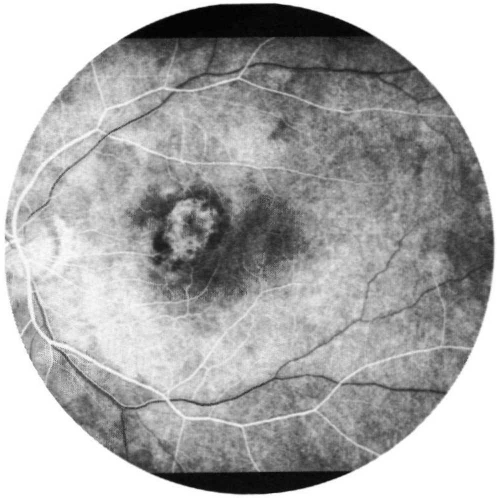
Detectable areas of irregular elevation of the RPE (well- or poorly demarcated) that all show stippled hyperfluorescence within 1 to 2 minutes after dye injection, with persistent staining or leakage in the late phase after 8 to 10 minutes (Figure 5)

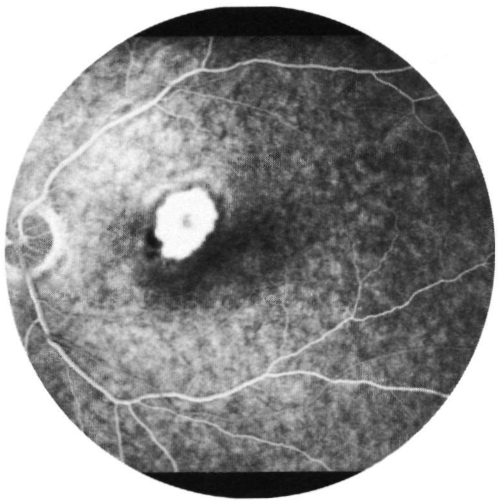
Type II Late leakage of undetermined source:

Areas of late phase leakage at the level of the RPE without well-demarcated areas of hyperfluorescence discernable in the early phase that can account for the leakage

Definition of mixed CNV

A combination of classic and occult patterns in one CNV lesion





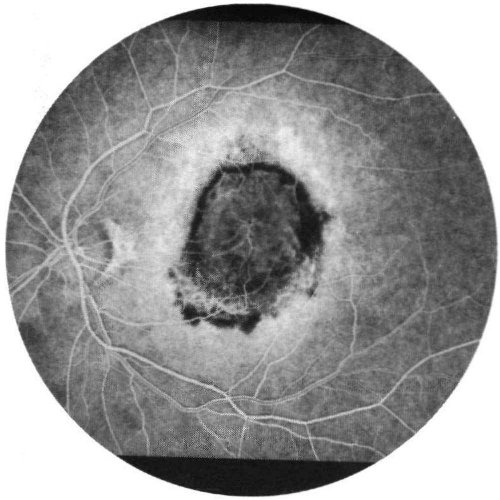
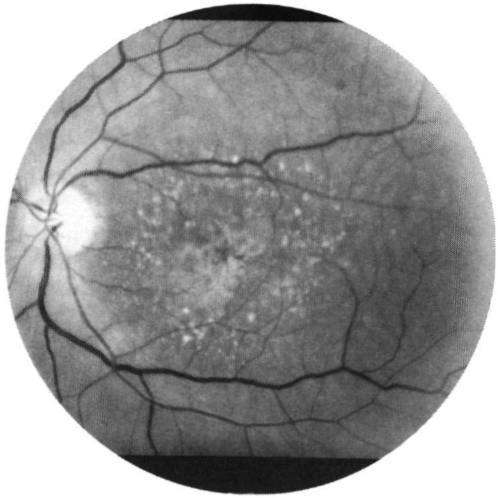
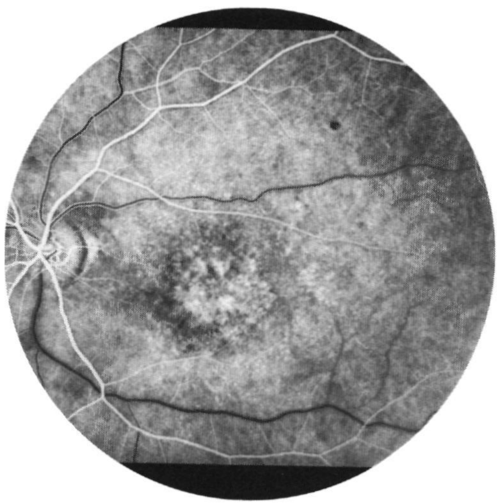


Figure 4. *The natural course of a classic CNV (left eye).*
***Top left**, early phase at presentation (1 DA). **Bottom left**, late phase at presentation. **Top right**, early phase after 6 months (3.5 DA). **Bottom right**, late phase after 6 months. Note the increase in lesion size and late leakage at 6 months.*





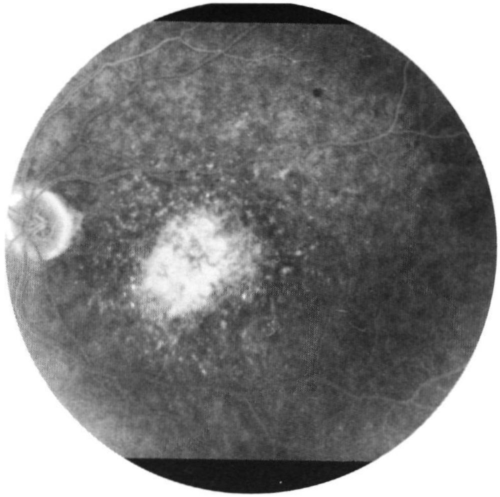


Figure 5. *Occult CNV type 1.* ***Top left,*** *red free of left eye.* ***Bottom left,*** *early phase, with stippled hyperfluorescence.* ***Top right,*** *late phase leakage.*

Hence, the terms "classic" and "occult" describe FA patterns. The pattern of CNV hyperfluorescence can be described as classic or occult. Well demarcated (well-defined) and poorly demarcated (poorly-defined) are terms to describe the bounderies of a classic or occult lesion (Figure 6). Poorly demarcated bounderies refer to bounderies of a lesion in which a portion of the entire interface between the lesion and the retina unaffected by any lesion component is not well defined. Well demarcated bounderies refer to bounderies of a lesion in which the interface between the lesion and the retina which is unaffected by any lesion component is well defined. Three features that can obscure the boundaries of CNV are: blood that blocks fluorescence through the late phase of the angiogram; elevated blocked fluorescence not corresponding to blood to be seen on color photographs corresponding to hyperplastic pigment or fibrous tissue; serous PED defined as uniform, circular or ovoid distinct detachment of the RPE with early, bright hyperfluorescence beneath a smooth dome-shaped elevation of RPE which in the late stages increases in intensity in a bright, homogenous, and well demarcated pattern.

CNV		
1. Classic	*2. Occult* *Type I* *Type II*	*3. Mixed*
Boundaries		
a. Well-demarcated = Well-defined		*b. Poorly-demarcated = Poorly-defined (blood, elevated blocked fluorescence, serous pigment epithelial detachment)*

Figure 6. *Fluorescein angiographic patterns of CNV.*

In case of subfoveal CNV there are many additional diagnostic modalities. For example, indocyanine green (ICG) angiography is often used in case of occult CNV [88,89,90,91,92,93,94]. ICG is highly bound to plasma proteins (98 %) and is a dye that absorbs and reflects light in the near infrared range permitting visualisation of choroidal detail not visualised by FA. Its main clinical application has been the ability to identify occult CNV. With the use of ICG angiography it is possible to convert occult CNV on FA to classic CNV on ICG in about 40 % of the cases. However a contribution to a better VA outcome after laser photocoagulation has not been established by this tool [93,94]. It is interesting that not all cases of classic CNV diagnosed with FA fluorescence with ICG, which suggests that some CNV lesions may leak fluorescein but not protein bound ICG. The underlying pathogenesis of ICG hyperfluoresence is not fully understood. An understanding of what ICG images represent requires further clinicopathologic correlation [93,94].

Another new diagnostic development is a combination of ICG angiography and microperimetry using the scanning laser ophthalmoscope which allows testing of the preferred locus for fixation with direct visualisation of both the test stimuli and the fundus [93]. Although the above mentioned techniques are interesting, the main diagnostic tool in case of subfoveal age-related CNV remains the FA pattern.

2.6 NATURAL HISTORY, TREATMENT AND EXPERIMENTAL THERAPIES

Natural history

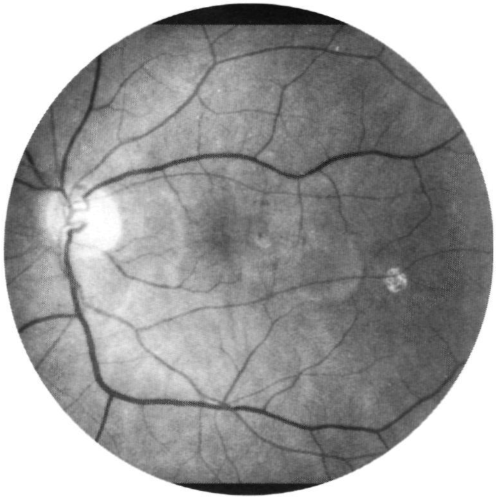
The deterioration of the VA is related to the rate of subfoveal leakage, the amount of subfoveal fluid and the subsequent photoreceptor loss The leakage depends, among others, on the growth speed of the newly formed subretinal vessels The growth rate of CNV in AMD has been estimated to an average of 9-10 um per day [68] However differences in growth rate, amount of leakage and subsequent rate of visual loss can be observed The rate of visual loss in a patient presenting with subfoveal CNV remains unpredictable but is partly dependent on the type of CNV (classic, mixed or occult) at presentation The natural course of subfoveal CNV is charaterised on FA by an increase in size of the membrane and an increase in late phase leakage over time (Figure 4 and 7)

There was no consistent approach in describing fluorescein patterns in case of CNV before the MPS definitions The results of the following studies cannot always be fully compared with each other

A study by Singerman et al determined the poor natural history of occult subfoveal CNV with a PED in AMD At one year follow-up of 55 eyes, 65 % had a VA less than 0 1 and 26 % even less than 0 05, 94 % of the patients developed a final VA of 0 1 or worse [99] Another study of the natural course of occult CNV by Bressler et al showed a severe decline in VA in 63 % of eyes after 12 months [96] The natural course of occult CNV was also determined in a prospective study New lesions occurred in 50 6 % of the eyes (n=79) and the incidence of visual loss by 2 lines or more was 33 % after 2 years [100]

Spontaneous regression of CNVs is extremely rare and occurs in less than 1 % of cases [101]

Soubrane et al described the poor natural course of CNV with subretinal hemorrhage [102] Patients with extensive subfoveal hemorrhages in occult CNV in AMD and without laser treatment will develop severe visual loss in 80 % of the eyes (n = 68) with a mean final VA of only 0 02 [103] A retrospective review of data of subfoveal hemorrhage in AMD revealed a progressive loss of VA from baseline in most eyes after 3 years After 6 months and 12 months, the VA decreased in 75 % and 69 % respectively [104]



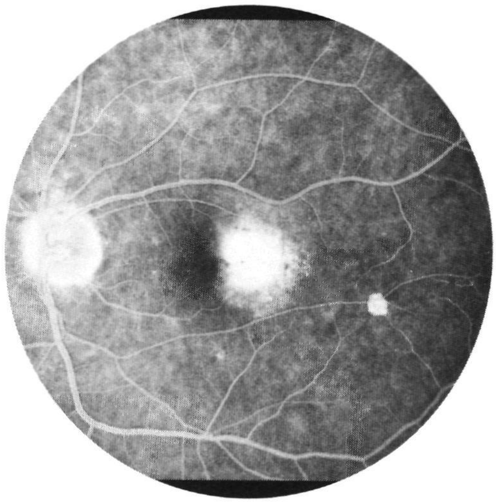


Figure 7. *Natural course of mixed CNV.*
Top left, *red free at presentation.* ***Bottom left,*** *late phase at presentation.* ***Top right,*** *red free after 6 months.* ***Bottom right,*** *late phase after 6 months. Note an increase in lesion size and late phase leakage.*

Detailed information concerning the natural course of classic subfoveal CNV, eligible for laser treatment, is provided by the MPS-group [8-18] Only subfoveal lesions smaller than 3 5 DA were included because, in case of treatment, large lesions would leave too few perifoveal photoreceptors unaffected to allow for useful vision The VA after 3 and 12 months follow-up, in untreated eyes with a small CNV (DA 1 or less) and an initially VA of 0 2 or better, declined to 0 16 or less in 58 % and 78 % respectively [12] For lesions with an initial medium size (>1 DA and <2 DA), a decline in VA after 3 and 12 months was found in 67 % and 79 % respectively [12] In 1986 the MPS-group also started a randomised trial of laser treatment versus no treatment in classic subfoveal CNV The change in visual acuity in the no-treatment group from the initial visit to 3 and 24 months was estimated After three months of follow-up respectively 52 2 % (n=178), and after 24 months 82 1 % (n=112) lost more than 2 lines of VA

Other results concerning the natural history of classic and occult subfoveal CNV became available during a multi-center randomised study on the effect of Interferon in cases of AMD [128] In a total group of 112 eyes, 58 % of classic CNV, 35 % of occult CNV and 37 % of mixed CNV, lost 3 or more lines of VA at 1 year follow-up Concerning the size of the CNV it was concluded that the area in disc diameters doubled in six months in the classic CNV group and doubled in 12 months in the occult and the mixed group In the classic group the size of the CNV did not increase between 6 and 12 months follow up [128]

The prognosis of the fellow eyes of patients with one eye affected with CNV secondary to AMD depends on the presence of 5 or more drusen, focal hyperpigmentation and definite systemic hypertension Estimated five year incidence rates ranged from 7 % for the subgroup of fellow eyes with no risk factors to 87 % for those with all 3 risk factors [129]

In conclusion, when a CNV is initially present within the avascular foveal zone the VA will become 0 1 or worse in 70-80 % of the affected eyes within 18 months [2,94] Visual loss is often rapid and foveal involvement at presentation is seen in 90 % of cases [2,94]

Treatment

During the last two decades, if patients with neovascular AMD were treated, they have mostly received laser treatment, although several experimental modalities have been applied as well [8-18] All these types of therapy will be discussed in this paragraph, apart from the application of radiation therapy, which is the subject of the following chapters With regard to laser treatment, no differences have been found between the efficacy of Argon red or green, yellow Dye or Diode laser wavelengths in treating CNV In the past very often laser photocoagulation of CNV was incomplete, because the occult part was not treated In general, temporary regression of an untreated part of CNV can occur within 3 months after laser therapy, however activation or relapse often develops after this period (personal communication Bressler NM)

The pattern of visual loss for new subfoveal lesions is influenced by the initial lesion size and the initial VA Laser photocoagulation therapy is only recommanded for small CNV lesions (< 1 DA) with a poor VA (0 1 or less) at presentation The patient must accept an immediate decrease in VA, but after 2 years his VA will be better compared with no treatment, because of the smaller central scotoma An ultimate benefit of only one Snellen line was seen after 18 months of follow-up in laser treated patients compared with a control group Treated eyes experiences an immediate decrease in VA (3 lines on average) so the patient and the ophthalmologist must be thoroughly prepared

An analysis from the patient's perspective by Bernstein et al revealed a strong preverence for laser intervention by patients with eligible subfoveal CNV, despite this risk of immediate visual loss [105] However, opinions differ on the question whether it is preferable to have a marginal long-term benefit, starting 18 months later, at the cost of a significant deterioration immediately after treatment, rather than this impairment developing over a period of years

In eyes with subfoveal CNV, foveal-sparing laser photocoagulation has been proposed as an alternative modality [105] In a pilot study stabilisation of the pre-treatment VA in 60 % of eyes (n=40) after one year has been noticed after scatter photocoagulation of subfoveal CNV [107] Comparable results have been noted by Coscas et al after perifoveal laser treatment for age-related subfoveal AMD [108] However recurrences of a CNV after laser therapy occur unfortunately in about 50 % of initially well treated eyes A study by Soubrane et al has shown that in case of occult CNV, laser therapy results in a worse outcome in terms of final VA when compared to no treatment [104]

A large proportion of patients (87 %) with CNV, occult CNV in particular, do not meet MPS guidelines and therefore only 13 % of the patients with classic well-defined CNV appear eligible for laser treatment [77]

Experimental therapies

ICG-guided laser treatment

ICG angiography is a new experimental diagnostic procedure for visualizing normal and abnormal choroidal blood vessels However the fact that treatment to areas of hyperfluorescence on FA can be beneficial does not mean that treatment to areas of hyperfluorescence on ICG should be beneficial as well The gold standard for imaging CNV remains FA and it has been shown that no patient is being deprived by not having access to ICG angiography [109,110]

Submacular surgery

Many reports have been published concerning the removal of subfoveal neovascular membranes [113-119] Preliminary clinical experience with the surgical removal of subfoveal CNV suggests that central vision may be restored in eyes with CNV due to presumed ocular histoplasmosis syndrome and to idiopathic causes [115] However disappointing results have been reported concerning the results of surgical removal of subfoveal CNV in AMD This is probably due to the multiplicity of ingrowth sites of CNV in AMD and, consequently, the inevitable removal of vital RPE and often choriocapillaris during surgery Yet, it is still unclear at which point of the natural course the indication for surgery should be given and which method yields the best results, a clinical trial evaluating submacular surgery versus observation of subfoveal CNV has been planned An experimental surgical procedure introduced by Machemer, macular translocation, did result in improved monocular vision [120]

RPE transplantation

An experimental approach of transplanting fetal RPE-cells under the macula resulted in survival of these cells for as long as 3 months [121] In cases of exudative AMD no positive effect on the visual loss was observed

Photodynamic therapy and benzoporphyrin-lipoprotein

The application of photodynamic therapy, using lipoprotein-delivered benzoporphyrin derivate mono-acid photosensitizing dye administered intravenously, resulted in the closure of experimental CNV's in monkeys [122] A multicenter clinical trial has been started comparing this type of therapy with the application of diode laser and benzoporphyrin derivate and placebo in patients with mixed type subfoveal CNV in AMD

Pharmacologic therapy

1. Interferon α

A prospective randomized study has recently been ended because Interferon-α-2a provided no benefit as a treatment for CNV in AMD Although pilot studies demonstrated a stabilisation of CNV's during this therapy [123]

2. Thalidomide

As a potent inhibitor of corneal neovascularisation in mice, Thalidomide is at present used in small pilot studies for patients with neovascular AMD [128]

3. Anti-vascular endothelial growth factor

So far, there has only been gained experience with the administration of monoclonal antibodies inhibiting vascular endothelial growth factor in a monkey model [128]

Treatment of drusen

Knowing that hyperfluorescent soft drusen are at risk for developing exudative AMD, laser therapy is performed in an attempt to alter the natural course [124-126] In a study by Figueroa et al drusen dissapeared within 3 5 months after laser therapy, without complications [125] It is thought that laser stimulates macrophages and other phagocytic cells that can cause drusen to disappear and that it may destroy deteriorated RPE cells However, it remains questionable if the treatment of drusen indeed results in a reduced risk of CNV development

Vitamins and Zinc

The National Eye Institute in the USA has recently begun a multi-year study of the clinical course and prognosis of AMD including a trial component to evaluate the effect of vitamins, carotenoids and mineral supplements on the development of AMD [128]

Experimental treatment of subretinal new vessels using hyperthermia is under investigation (personal communication)

In conclusion, it is increasingly evident that laser treatment nor any of the above mentioned therapies will significantly reduce the severe visual loss experienced by most patients with this neovascular macular disease. Again it is important to emphasize that AMD virtually never leads to total blindness and that, often with the use of low-vision aids, even the patient affected in both eyes remains visual function [109,110]. In patients with central scotoma an eccentric retinal fixation area of sufficient size is necessary to regain reading ability by magnifying visual aids i.e. low-vision aids. Still, the social cost of this visual handicap is high and it is important to move forward in the management of AMD, especially since it is likely that in the future, as the population ages, ophthalmologists will be examining increasing numbers of these patients The knowledge gained by studying the influence of radiation therapy on AMD will be important, independently of the outcome [127].

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CHAPTER 3

RADIOTHERAPY

3.1 BACKGROUND

Introduction

Tissue damage by ionising radiation with electromagnetic photons (gamma- and roentgen or X-rays) results from energy absorption of the various cells [1,2,3,4]. After irradiation of biological tissue three phases can be observed. First the physical phase consists of interactions between charged particles and the atoms of which the tissue is composed. The chemical phase (second phase) describes the period in which the damaged atoms and molecules react with other cellular components leading to free radicals. Free radicals interact with macromolecules within the cell to produce molecular changes, mainly in the chromosomal DNA. As a result irradiation acts on the replicative mechanism of cells. The third phase, the biological phase, begins with repair of damaged DNA and death of stem cells as early reactions ending up with late reactions including radiation carcinogenesis. Damaged DNA is responsible for the loss of the dividing capacity of the cell, although the cell may remain its normal biochemical function and normal morphological structure. The survival of a sterilised cell depends on its proliferative activity, because the damage only becomes visible after the next cell division.

Tissues

A tissue consists of a group of differentiated cells with a specific metabolic function. Specialised cell types with a specific function can cooperate in an organ, like for example liver cells. An increase in the amount of cells is not only necessary for tissue growth during development, but also to replace the loss of dead cells or cells lost during differentation. Tissues can be catagorized according to their cell dividing activity in either type-H (hierarchical) or type F (flexible) tissues [1,2,4,5]. In type-H tissues, cell populations for cell renewal and function are separated in different compartments (Figure 1 a). For example in the skin, stem cells divide and become either proliferating cells or new stem cells. The fast dividing proliferating cells eventually mature into differentiating transit cells and mature post-mitotic functional epithelial cells. Liver on the other hand is an example of a type-F tissue because it has functional cells that are also capable of self renewal (Figure 1 b). F-type tissues have a less recognisable separation into different compartments and functional cells maintain their capacity of proliferation

Stem cells ← **Stem cells** (self-renewing) → Precursors → Mature cells

Figure 1 a. *Hierarchical tissues Tissues with a recognisable separation between the stemcell compartment, an amplification compartment and a post-mitotic compartment of mature functional cells*

Stem cells ↔ Mature functional cells

Figure 1 b. *Flexible tissues Tissues without a recognisable separation between these compartments Functional cells have the capacity of renewal*

Radiation effects

Between the various cell types a difference exists in cell survival after a radiation dose After irradiation cells may not be affected at all, may be affected but their damage can be completely repaired or are affected and show cell death either mitotic or apoptotic Often cells have the possibility to repair the radiation damage and maintain their biochemical function, but have lost the possibility to divide These cells are sterilised and biologically death, because they cannot proliferate anymore Mitotic death occurs when the sterilised cell attempts to divide In case of fast dividing tissues, an early radiation effect is noticed, while slow dividing tissues express radiation damage after a longer lag time [1,2,3,4,5]

Apoptosis is a physiological mechanism of cell death that is genetically regulated and contributes to the balance between cell growth, differentiation and maintenance of normal tissues [4,5] Interphase death occurs unrelated to the cell cycle in irradiated nonproliferating cells by apoptosis, a natural programmed cell death, necessary for the elimination of genetic abnormalities [1,2,4,5]

Radiation may lead to single-strand DNA breaks and double-strand DNA breaks The number of lesions induced by radiation in DNA is greater than those that lead to cell killing Cells are able to repair radiation-induced single-stranded DNA breaks Breaks in double strand DNA is the most common type of radiation lesions that lead to cell death Residual DNA double-stranded breaks which the cell fails to repair are regarded as those that lead to radiation induced cell death Several studies have suggested that radiation damage to the least active regions of the genome, such as those which reside within heterochromatin, may be the most critical for cell survival [1,2,3,4,5,6,7,8] It is hypothesized that DNA involved in synthesis is more accessible to repair enzymes than inactive regions located within tightly bound heterochromatin or mitotic chromosomes The human retinal vascular endothelial cells are distinctively heterochromatic, with the bulk of the chromatin around the nuclear envelope, resulting in much more radiosensivity than for example the inner retinal neurones whose nuclei are highly euchromatic It is known that the highly heterochromatic nuclei of rat photoreceptor cells are exquisitely sensitive to ionising radiation compared to those of primates that are more euchromatic [3,7,8,9,10]

Tissue response

After irradiation, fast dividing tissues will express radiation damage within days to weeks Therefore these tissues are called acute responding tissue Damage occurs when the functional cell compartment is not replaced by new cells because of radiation induced cell death of the proliferating cells The natural loss of functional cells is not compensated for Tissues depending for their integrity on continuous cell proliferation will be damaged early by irradiation [1,2,4,5] Early damage (from weeks to months) may be followed by late types of damage, often with a vascular basis In the skin acute epidermal reactions may be followed by late vascular reactions, like fibrosis and atrophy Slow dividing tissues, for example vascular endothelial cells, may retain latent radiation damage until its expression at mitosis These tissues are called late responding tissues In H-type tissues, the time between irradiation and tissue response is dose-independent and related to the life-span of the functional cells The rate of recovery, however, is dose-dependent and related to the number of surviving stem cells

Principles of radiobiology: the 5 R's.

The biological factors that influence the response of tissue to fractionated radiotherapy are known as the 5 R's of radiobiology [1,2,4,5] The 5 R's of radiobiology affect both normal tissue and malignant cells

1 Radiosensitivity

There is a difference by nature between various types of cells and tissues concerning the susceptibility of radiation known as the intrinsic radiosensitivity A certain dose damages more cells in sensitive tissues than the same dose does in resistant tissues For example malignant lymphoma cells are very radiosensitive, while glioblastoma cells are radioresistant

2 *Repair capacity*

Cells may repair radiation damage when they are given time to do so, resulting in maintainance of the cell function and cell proliferation The amount of sublethal damage depends on the tissue type and the radiation dose and can accumulate and become lethal The capability of repair of sublethal damage strongly differs between various cell types, but most damage is repairable if the cell is left for hours before the next dose is administered If this phenomena is more pronounced in normal than in target tissue, fractionated irradiation leads to a better therapeutic effect with less side effects

3 *Repopulation*

As a reaction to cell death caused by irradiation, clonogenic stem cells start accelerated proliferation to produce new cells rapidly A rest period during fractionated radiotherapy is accompanied by repopulation of target cells and surrounding tissue Cells that survive irradiation proliferate and thus increase the number of cells that must be killed In case of fast dividing cells, repopulation during the time between two fractions, results in a loss of radiation effect

4 *Reoxygenation*

Radiation kills viable oxic cells preferentially and anoxic cells may be rescued, resulting in more hypoxic cells surviving after a dose of radiation Because death oxic cells disappear, a decrease in distance between hypoxic cells and capillaries occurs with an increase of oxygen flux towards hypoxic cells Fractionated irradiation results in a smaller proportion of surviving hypoxic cells Reoxygenation means that fractionated radiation leads to a shift of cells out of the hypoxic cell compartment towards the well oxygenated group, resulting in a higher irradiation effect

5 *Redistribution*

In general, the effect of radiation on a cell is low during the S-phase (= DNA synthesis) of the cell-cycle and the highest just before mitosis (= M-phase) Cells in M-phase will be more damaged resulting in a relative increase of cells in S-phase Cells that survive a first dose of radiation will tend to be in a resistant phase (S-phase) of the cell cycle and within a few hours they may progress into a more sensitive phase (M-phase) This means cells synchronise and reach the M-phase at the same time This phenomena is called redistribution The time between fractions can be influenced to profit of this redistribution

Physical factors that influence the radiation sensitivity

Clinically the main factors that influence the development of radiation damage are

1 Total radiation dose and fraction size

The radiation dose is the kinetic energy released to material and is expressed in Gray [1 Gray (Gy) = 1 joule/kg = 100 rad]

It is important to recognize that comparison of a total radiation dose between two types of fractionated treatment is dependent on the biological effect [1,2,4,5] Considering a tissue with a specific radiosensitivity, it will have for example 10 stem cells left after a dose of 10 Gy in one fraction, while after 10 Gy in two fractions of 5 Gy, the amount of stem cells, capable of growth, will be 15 The same total dose (10 Gy) leads to a difference in biological effect (10 versus 15 stem cells left) In general, a dose given in one fraction leads to less surviving cells than the same dose given in two or more fractions, e g fractionation allows a higher dose to be administered

The linear-quadratic model, LQ model, is developed for comparing the relation between the dose per fraction, the total dose and the biological effect on tissue [4,5] In general, the surviving fraction of target cells decreases with an increase of the administered radiation dose The surviving fraction (SF) after a dose per fraction d is given by $SF= \exp(-\alpha d-\beta d^2)$ The α-component (linear component) determines the cell survival curve after low dose irradiation, but at higher dose the quadratic β-component is the most important A cell survival curve is the relation between the dose and the fraction of surviving colony forming cells The relation between the radiation dose and the fraction of surviving cells is shown in figure 2 Clonogenic cells are cells that are able to form in vitro colonies exceeding 50 cells (representing 5-6 divisions) The shape of the curve depends, among others, on the cell type, the radiation type and the time between fractions Cell survival curves show lower efficacy of killing at lower doses, before exponential cell killing is demonstrated at higher doses, so they are characterized by a "shoulder" on a semi-logaritmic scale

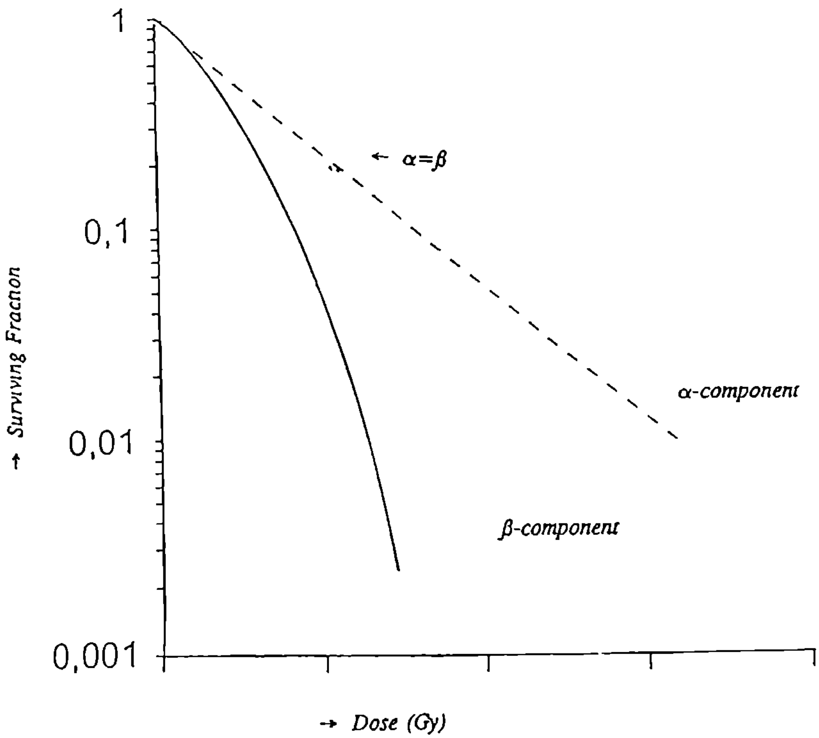

Figure 2. *Cell surviving curve (black line) Relation between the radiation dose and the fraction of surviving cells The α-component predominates at low dose and the β-component predominates at higher dose Dose in which the α-contribution equals the β contribution α=β X-axis Radiation dose (Gy), Y-axis Surviving cell fraction*

The α/ß ratio, experimentally obtained for the various tissues, describes the shape of the fractionation response, a low α/ß ratio (1-4 Gy) for example in liver and bloodvessels, is characteristic of late-responding tissue (lag time= 0 5-5 years) A low α/ß ratio corresponds to a cell survival curve with a strong quadratic component and steep curve because of a relative large ß influence Fractionated irradiation leads in case of a low α/β ratio, to less radiation damage and a greater repair Repair of sublethal damage can be measured by the increase in dose necessary to obtain biologically the same effect A small α/β ratio indicates a large susceptibility to fractionation and a large repair capacity From clinical experience it is known that a change in the number of fractions, with a subsequent change in the dose per fraction, has no effect on early reactions, however radiotherapy with fewer larger fractions give an increase in late effects Hence, the sensitivity to large fraction sizes is much higher for late-responding tissues than for early-responding tissues

The α/β ratio of normal tissue is related to the time between irradiation and the moment of tissue reaction (Figure 3) Early responding tissues, between 3-9 weeks, are characterised a high α/β ratio (10 Gy), like skin, with actively proliferating stem cells

	Early reactions	Late reactions
latency time	between 3-9 weeks	between 0 5-5 years
fractionation susceptibility	Low	High
sensitivity	α/β = 10-25 Gy	α/β = 1-4 Gy

Figure 3. *Characteristics of early and late responding tissues*

The effect of fraction size and total dose will be illustrated in the following example The biological effect of a total dose of 24 Gy administered in 12 fractions of 2 Gy is not the same as a total dose of 24 Gy in 4 fractions of 6 Gy For example Current treatment for subfoveal CNV is 4 fractions of 6 Gy per day resulting in a total dose of 24 Gy How many fractions of 2 Gy give the same biological effect, presumed an α/β ratio of 2 Gy ?

Formulas

LQ-model $\quad RE = 1 + \dfrac{d}{\alpha/\beta(2,5)}$

Dtol = ETD/RE

RE = relative effectiveness per dose

d = dose per fraction

Dtol = tolerance dose with dose per fraction d

ETD = extrapolated total dose = extrapolated tolerance dose

α/β ratio = specific for each tissue

Dtol = 6 Gy 4 = 24 Gy

RE = 1 + 6/2 = 4

ETD = 24 4 = 96 Gy

d = 2 RE = 1 + 2/2 = 2

Dtol = 96/2 = 48 Gy

48 / 2 = 24 fractions

In conclusion 4 fractions of 6 Gy per day causes more or less the same biological effect of 24 conventional fractions of 2 Gy, according to the LQ-model with a presumed α/β ratio of 2 Gy

2 Time factor

The overall treatment time, the time between the first and last fraction, during radiotherapy is of importance mainly for acute reactions, rather than for late reactions However the time factor is rather complex and depends on the dose per fraction, the interfraction interval and on the tissue type In general, a total dose administered in 6 weeks is more effective than the same dose given in 12 weeks The underlying phenomenon responsible for this observation is repopulation Surviving cells start to divide when the time between 2 fractions is longer than approximately 24 hours This results in an increased cell number, needing an increase in total dose For late reactions in normal tissues, no appreciable difference can be found between a short or a longer treatment time

3 The irradiated volume

The size of the radiation field is responsible for the volume-effect In general the tissue tolerance decreases with increasing treatment volume Midena et al concluded that radiation retinopathy has a higher incidence and a lower latent time when the whole eye is irradiated including the peripheral chorioretina [12]

4 Concurrent chemotherapy

Combined radiation and chemotherapy can result in retinal damage and remarkable vasculopathy after a total dose, which under normal circumstances (without chemotherapy), would not be harmfull

5 Systemic conditions

There is a synergistic association between ionising radiation and the diabetic state Radiation vasculopathy tends to occur earlier and to be more severe in diabetes patients Radiation retinopathy and diabetic retinopathy are both occlusive micrangiopathic diseases and therefore may have a synergistic effect Radiation retinopathy occurs more frequently in diabetes patients compared with controls Thus it is clear that diabetes as well as collagen diseases negatively infuence the effect of irradiation of the eye [1,2,3,4,5,10,11,12,13]

3.2 VASCULAR GENESIS AND PATHOGENESIS

The term angiogenesis describes the generation of new blood capillaries from preexisting vessels which occur in both normal situations, for example wound healing, and in pathological situations like in neovascular AMD [14,15] The normal architecture of human capillaries consists of endothelial cells with pericytes The morphologic steps occurring during capillary neovascularisation in rabbit corneae include degradation of the preexisting vessel basement membrane by proteolytic enzymes Stimulated endothelial cells migrate towards the angiogenic stimulus and begin to proliferate Capillary lumen is created by curving of endothelial cells and after new basement membrane formation blood flow begins [14,15]

Histological examination with electron microscopy of human eyes showed an endothelial cell sprout, originating from the choriocapillaris, passing through a narrow gap in Bruch's membrane in 6 eyes with exudative AMD [16] The tip of the endothelial sprout was surrounded by enlarged pericytes and the endothelial cells were thickened and irregular This supports the hypothesis that pericyte mobilisation may accompany endothelial cell migration in angiogenesis in intrachoroidal new vessel formation [16]

Angiogenesis is required for tissue repair in the adult but is also responsible for a variety of pathologic disorders Studies in experimental oncology have shown that angiogenesis is necessary for primary tumour growth, progression and metastasis [15] Tumours are, in general, angiogenesis-dependent diseases This means that angiogenesis is necessary for primary tumor growth, progression and metastasis and that its inhibition may lead to tumor remission [15] It has been proven that many bioactive products, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-beta (TGF-ß), macrophages and endothelin-1 promote angiogenesis in various models, but the relationship between this activity and the regulation of blood vessel growth is not fully understood [17,18,19]. Endothelial cells not only respond to tumour secreted growth factors, but also actively stimulate tumour cell proliferation through production of these soluble growth factors [15,17,18]. Angiogenesis inhibitors, suppressing neovascularisation of tumors, have an important role in tumor remission [17]. Anti-angiogenic drugs like Interferons, Thalidomide and Tamoxifen are inhibitors of endothelial cell proliferation.

In ophthalmology, intra-ocular neovascularisation is observed in patients with for example diabetes mellitus, central retinal vein occlusions and exudative macular degeneration. Retinal neovascularisation occurs after the release of angiogenic factors by the ischaemic retina [14,15]. Elevations of VEGF levels in the vitreous humor of eyes with proliferative retinopathy have been described [14,15,17]. That VEGF levels correlate with ocular angiogenesis is supported by the report that intra-ocular administration of anti-VEGF antibodies inhibits the iris neovascularisation following central retinal vein occlusion in a primate model [17]. Immunohistochemical localisation of VEGF in surgically resected neovascular membranes raises the possibility that it is also a mediator of neovascularisation in exudative AMD [17]. It is speculated that the normal retinal glial cells and retinal pigment epithelial cells produce VEGF, necessary for maintaining the normal structure and function of retinal capillaries and choriocapillaris [14,17].

The normal regulation of angiogenesis is influenced by stimulating and inhibiting factors, but how angiogenic factors are released and influenced is largely unknown. Although the pathogenesis of choroidal neovascularisation is still under investigation, macrophages and pigment epithelial cells are thought to play a role during angiogenesis by releasing factors, including VEGF. However, the endothelial cells of the neovascular membrane itself may synthesize VEGF [14,17,19].

3.3 RADIATION RESPONSE OF VASCULAR TISSUE

Investigations concerning endothelial cell survival in vitro have shown the large radiosensitivity of endothelial cells compared with other cell types, for example pericytes, constituting the vessel wall [3,4] After irradiation of endothelial cells it is important to know the relative number of endothelial cells required to preserve tissue function On the basis of cell survival determination it is estimated that with only one in ten endothelial cells surviving, the tissue may survive [4] The remaining endothelial cells have been shown to spread and to cover a larger area of the vessel wall [4]

Archer and co-workers studied the earliest microvascular changes after a wide range of single dosis radiation (2 20 Gy) in the retinae of the Lister rat, which vasculature is comparable to the human [6,8] The changes were most evident between 6 and 12 months after exposure to 15-20 Gy, and the earliest observable pathology was elongation of the capillary endothelial cell nuclei and narrowing of the capillary lumen More affected vessels showed endothelial cell loss and capillary closure The retinal pigment epithelium and choroidal circulation were less radiosensitive

Morphological changes occur chronologically in human capillaries after irradiation with a single dose of 8 7 Gy [2] Within hours vasodilatation and loss of vasomotion occurs, with swelling and vacuolation of the cytoplasm of endothelial cells Clusters of platelets attach to damaged endothelial cell sites and interrupt the blood flow in some vessels Within weeks, loss of endothelial nuclei can be observed, with a reduction in the number and length of the capillaries and occlusive changes Late effects after months to years are teleangiectasia and proliferation of endothelial cells and fibrosis [1,2,3,6,8]

During the natural course of eyes with subfoveal CNV, fibrovascular scar development shows similarities with the normal wound healing process In general, acute inflammation, invasion with polymorphonuclear leucocytes transforming to macrophages, fibroblasts and the newly formed capillaries are all part of the wound healing process In a study determining the effect of irradiation of ocular wounds, suppressing of mononuclear cell division was noticed after local wound irradiation [9] Furthermore, it was concluded that irradiation of ocular wounds affected inflammation both qualitively and quantitively and limited intraocular cellular proliferation [9]

3.4 SIDE-EFFECTS

Introduction

As the lag time of response of normal tissues to therapeutic radiation exposure varies from one type of tissue to another, irradiation with X-rays can result in the occurrence of acute, subacute and/or late effects. All components of the eye can be affected by radiation, but it is clear that the various tissues have different radiosensitivities. The mature retina is relatively resistant to clinical doses of radiation because of its stable population of nerve cells [3]. One should be aware that there is a tenfold difference in dose between the cataract threshold and the dose required to damage the retina [27].
Despite improvements in radiotherapeutic methods such as shielding and lens-sparing techniques, it is often difficult to treat the target-tissue without irradiating the lens. The eye and ocular adnexa are vulnerable to ionising radiation with a different susceptibility of the various tissues. The late effects of irradiation of the eye are known from patients treated for ocular disease but also from those treated for diseases of the central nervous system and of the ear-nose-throat region.

Side-effects

Acute and late effects of radiation on the eye and ocular adnexa, and tolerance levels of the various ocular structures are well known from many studies [3,6,15,10,11,12]. However, it is difficult to evaluate the literature data on ocular radiation morbidity because of differences in treatment planning and problems to assess the exact radiation dose actually delivered to the eye after for example treating the central nervous system, orbit or para-nasal sinuses. Recently, a consensus conference was held on the radiation-induced pathophysiological and clinical changes of the various ocular structures as well as dose-response data and management of ocular complications [13]. When establishing dose-effect data, it is important to distinguish between a single or a few large radiation fractions versus multiple small conventional fractions. A conventional fraction size of 2.0 Gy/day is commonly considered a standard fraction. Larger fractions are generally more damaging than the same dose delivered with conventional irradiation [3] (see page 65; the LQ-model).

Ocular adnexa and anterior segment

Acute reactions following radiotherapy include hyperaemia of the conjunctiva and erythema beginning after a few days and resolving within 2 to 4 weeks Eyelids react to radiation similar to skin, with erythema after 30 40 Gy in conventional fractions, which is almost always self-limiting Permanent epilation of eyelashes is observed after a radiation dose in excess of 50 Gy in conventional fractions Conjunctivitis may develop during radiation in the range of 50 Gy Punctate keratitis, a superficial lesion of the cornea epithelium, can occur after doses with 30-50 Gy in 4 weeks

A severe late complication is the so-called "dry-eye syndrome" Concerning the lacrimal gland the majority of patients tolerate doses in the range of 30-40 Gy to the field of the entire orbit, but atrophy may occur with doses of 50-60 Gy Corneal ulceration has been seen after doses exceeding 60 Gy Keratitis with corneal ulceration can occur after 30 Gy in large fractions, but is avoided when conventional fractionation is used with a total dose less than 50 Gy Symblepharon has only been described after 80-100 Gy The sclera is resistent to radiation but late damage has been reported after 1000 Gy to the posterior sclera from Ruthenium plaques

The lens

A loss of normal transparency of the lens, that is cataract, can be a late effect after ocular irradiation The latent period between irradiation and cataract formation decreases as the dose increases The lens is more susceptible to radiation induced cataractogenesis in younger than in older patients Radiation cataract usually presents first as a posterior subcapsular opacification, however, a minority develops anterior subcapsular opacification Fractionated radiation doses of 2 Gy on the center of the lens, exceeding 12 Gy total dose, will cause cataract However, the mean latency time after lens doses of 4-10 Gy is about 6 5 years A single dose of 10 Gy is believed to be responsible for cataract development in 80 % of irradiated eyes [13]

The retina and choroid

Radiation induced acute ultrastructural effects in the retina include changes in rod photoreceptors and pigment epithelial cell damage with mitochondrial swelling [6,8] Radiation retinopathy i and usually occurs within 3 years after treatment The frequency and extent of radiation retinopathy depends on the total dose, fractionation, dose rate, beam energy combined with radiation field arrangement, and concurrent vascular disease or chemotherapy Although many factors influence the development of radiation retinopathy, the total dose and fractionation are the most important [10]

There are considerable difficulties in determining the exact amount of radiation received by the retina in patients having treatment for tumours of the paranasal sinuses, nasopharynx and cerebrum In the past many studies on radiation retinopathy were performed without CT treatment planning Retrospectively it is not always possible to estimate the retinal isodose curve after primary non-ocular treatment Differences in radiation beam direction, radiation field and fraction dose are all important For example, antral irradiation delivers a significant dose to the retina and optic nerve Sometimes the orbit may be involved in the radiation field because of extension of the tumor in the orbit [12] The earliest identifiable changes in the retinal microvasculature are focal capillary closure and irregular dilatation of the neighbouring microvasculature [3,6] Progressive occlusion of small retinal vessels with secundary ischemia and edema may occur Radiation retinopathy resembles diabetic and hypertensive retinopathy and is characterized by microaneurysms of the capillaries, cotton-wool spots, intraretinal hemorrhages and leakeage of retinal vessels with exudates [3,6,10,11]

Treatment of radiation retinopathy with laser photocoagulation is indicated in case of peripheral retinal ischaemia and neovascularisation, but is contra-indicated when severe macular ischaemia is present The addition of chemotherapy and the existence of diabetes mellitus may potentiate radiation retinopathy Merriam et al concluded that a cumulative dose of about 56 Gy, using daily fractions of 2 Gy, is related to a 5 % probability of late damage [20] Nakissa et al reported that all patients treated with doses over 45 Gy to the posterior pole had recognisable retinal changes, but decreased visual acuity occurred only in patients receiving over 65 Gy total dose [24] In most cases radiation retinopathy occurs 0 5 to 3 years after therapy [1] A study by Midena et al stressed the importance of radiation damage to the anterior choroidal circulation resulting in occlusive changes in the choriocapillaris [12] The term radiation chorioretinopathy is proposed instead of radiation retinopathy, because it better reflects the morphologic and clinical aspects of radiation damage to the chorioretina [12]

In conclusion, severe radiation retinopathy is not observed below a total dose of 50 Gy with recommended daily fractions that do not exceed 2 Gy in patients without vascular disease [3,6,10,11,12]

The optic nerve

A late radiation-induced effect is anterior optic neuropathy, presenting with a painless, sudden visual loss with progression over several months After a period of weeks to months the hemorrhagic disc swelling subsides, followed by optic disc palor Optic neuropathy can be expected, for example in patients treated with a total dose of 45-50 Gy for pituitary adenoma, with a fraction dose of more than 2 5 Gy [13] Several authors state that radiation optic neuropathy is a consequence of radiation retinopathy and occurs secondary to vascular injury [6]

The orbit

Late effects, e g bony hypoplasia with atrophic soft tissue changes, of radiation on the bony orbit and secondary neoplasms are primarily seen when radiotherapy is applied to the growing facial bones of children, as in the treatment of retinoblastoma and rhabdomyosarcoma [13] Surgical reconstruction of socket contractures includes eyelid surgery and the use of intraorbital implants

Side-effect	**Minimum total dose (Gy)**	**Acute or Late**
conjunctivitis	50 Gy	acute, within 4 weeks
eyelid erythema	30 - 40 Gy	acute, within 4 weeks
dry-eye syndrome	50 - 60 Gy	late, after > 1 year
cataract	4 - 10 Gy	late, after 6 5 years
radiation retinopathy	50 Gy	late, after 0 5 - 3 years
optic neuropathy	45 - 50 Gy	late, after > 1 year

Figure 4. *Acute and late side-effects of ocular irradiation*

3.5 RADIOTHERAPY FOR SUBFOVEAL CHOROIDAL NEOVASCULARISATION (CNV)

Introduction

The discovery of X-rays by Roentgen in 1895 and radium by Curie in 1898 was the start of the introduction of new therapeutic modalities in various diseases After 20 years of research, Rohrschneider was able to list the ocular structures in order of decreasing radiosensitivity lens, conjunctiva, cornea, uvea, retina, optic nerve [21] One of the first reports on radiotherapy for vascular ocular diseases was published by Guyton and Reese in 1948 [22] Their paper "Use of roentgen therapy for retinal diseases characterized by new-formed blood vessels" contains information on 14 patients with vasoproliferative retinal disease They concluded that in 6 eyes after a total dose of 100 Gy even the largest new vessels completely disappeared after 18 months of follow-up In a study treating 21 patients with Eales' disease, a retinal vascular disease with leakage, the value of irradiation was doubtful resulting in discontinuation of therapy [23]
Unfavorable results of roentgen treatment of the posterior ocular segment in proliferative diabetic retinopathy were published by Larsen, treating patients with diabetic retinopathy with a total dose of 27 Gy with a daily fraction dose of 1-2 Gy [24] Hayreh, in 1970, stressed the importance of fluorescein angiography in detecting the early microvascular changes in the retinal and choroidal vasculature after ocular irradiation [25] Already in 1930 Takahashi concluded, using histological methods, that newly developing capillaries in wound healing were very radiosensitive [26]

In modern ophthalmology, radiotherapy is used to treat a variety of diseases [27] Benign ocular conditions like juvenile xanthogranuloma of the iris and diffuse choroidal haemangiomas respond well to lens-sparing radiotherapy [28,29] Ruthenium-plaque therapy have become standard therapy for small to medium sized melanoma External beam radiotherapy or teletherapy for choroidal involvement of leukaemia and for metastasis from solid cancer, breast cancer in particular, is another example of the use of X-ray therapy for ocular diseases Graves' ophthalmopathy and retinoblastoma are ocular-related problems that can also be managed by use of modern radiotherapy techniques [30]

Recently radiotherapy has been introduced in cardiology to solve the problem of reststenosis after balloon angioplasty Clinical endovascular irradiation via a radioactive stent with doses of 12-20 Gy appear to be efficacious in the prevention of this [31] The mechanism of inhibition of neointimal formation is related to direct radiation effects on proliferating smooth muscle cells

Subfoveal Choroidal Neovascularisation (CNV)

The main objective using radiation for subfoveal CNV is to induce regression and promote inactivation of the subretinal neovasculature with subsequent reabsorption of fluid and blood and reduction of the subretinal fibrosis, without harming the neuroretina and retinal pigment epithelium (RPE)

Retinal vascular cells undergoing mitosis would be expected to be vulnerable when irradiated, and environmental factors, particulary the high oxygen tension on the arterial side of the circulation, contribute to the radiosensitivity of vascular endothelium Normal human capillaries are radiosensitive, expecting choroidal neovascular membranes to behave the same It remains difficult to predict the behavior of choroidal new vessels because the intrinsic radiosensitivity of these vessels is unknown The main objective using radiation is to induce regression of the CNV, reducing the leakage with subsequent reabsorption of subretinal fluid leading to small subretinal fibrosis It is hypothesized that radiotherapy may affect angiogenesis 1 directly by damaging neovascular endothelial cells and cytokine-producing macrophages resulting in mitotic death of these cells, 2 indirectly through effects on regulatory genes within cells which produce endothelial-growth regulating cytokines and, 3 by decreasing the inflammatory response with subsequent reduction of large scar formation [41,48]

The potential of radiation treatment to result in regression of subretinal new vessels, without destruction of the overlying retina has led to clinical studies concerning patients with exudative AMD In 1968, Felten published a dissertation "Ueber die Behandlung der feuchten Maculadegeneration durch fractionierte Roentgenbestrahlung des hinteren Augenpols' [32] A total radiation dose of 1 8 Gy in fractions of 0 3 Gy was applied to 295 eyes using 200 Kv with a field diameter of 3 cm After a follow-up of 6 months to 8 years (mean 3 years), it was concluded that 70 % of eyes showed no visual deterioration because of the therapeutic effect of radiation on the inflammation involved in the disciform response These investigations were performed without the use of angiograms with fluorescein injections

Since 1955 low-dose radiation therapy has been used by Bangerter et al in Switzerland treating patients with neovascular AMD and various other kinds of ocular diseases [33] Radiation treatment is installed with "schwache-, mittelstarke- und grenzdosierungen", dependend on the diagnosis Ocular disorders including retinitis centralis serosa, drusen maculopathy, high myopia and exudative macular degeneration have been treated with an increasing total dose of 7 5 Gy (schwach) in 1 fraction, 20 Gy (mittel) in 17 fractions and up to more than 20 Gy (grenzdosierung) in fractions of 2-3 Gy using 250 Kv and a field of 6 25 square cm It is stated that irradiation results in less inflammation, less vascular permeability and regression of neovascularisation Although interesting observations were described, there is no published report of this group concerning the efficacy of radiation treatment in any of the treated ocular diseases

The results of the studies concerning radiation treatment in patients with age-related subfoveal neovascular disease performed in the University Hospital Nijmegen will be described in the next chapters [34,35,36,37] During recent years the results of many pilot studies concerning irradiation of age-related subfoveal CNV have been published [38-49] The experiences from these studies are positive, but in general the patient population studied was small the follow-up period short and no control group was observed

The Belfast study group reported their results concerning irradiation of age-related subfoveal CNV through a single lateral port, with 10-15 Gy in 5-7 fractions using 6 MV photons [38,39] They included patients over 60 years of age, with subfoveal CNV membranes for less than 3 months duration On grounds of experimental evidence, radiation levels in excess of 9 Gy were expected to influence actively replicating vascular endothelial cells After 12 months of follow up 63 % of the patients (n=19) maintained a stable visual acuity (VA) with a regression of the CNV on fluorescein angiography (FA) They concluded that radiotherapy had an inhibitory effect on subretinal neovascularisation reflected in atrophy of neovascular capillaries and decreased fluorescein dye leakage on the angiogram at 12 months follow-up [38] No side-effects were observed The vaso-occlusive response became obvious as a shrinkage of new vessels at 6 months post-irradiation, but atrophy of the CNV occurred secondary to vascular endothelial cell death, local thrombosis, and capillary closure [38] The authors postulated that the radiosensitive macrophages deprived the new vessels of vital cytokines necessary for growth and maintainance In treated patients after a longer period of follow-up, a reduction in scar size (SS) was reported after a mean follow-up of 28 months [39] Scars in radiation treated eyes occupied an area that was approximately one third of that in untreated fellow eyes (3 8 versus 11 7 square mm) Furthermore distance VA in radiation treated eyes was significantly better than that of untreated fellow eyes [39] After 24 months of follow-up treated eyes lost on average 12 % of baseline VA, whereas eyes belonging to the untreated control group lost 75 % of baseline VA [46] There was no evidence of radiation induced retinopathy or optic neuropathy in any patient 2 years post-treatment

Finger et al described their experience with teletherapy (6 MV, total dose 12-15 Gy) and palladium 103 ophthalmic plaque brachytherapy (apex dose 12-15 Gy) for subretinal new vessels [41,48] They compared the intralesional, intraocular, and intracranial radiation dose distribution of each treatment modality Both treatments were associated with decreased hemorrhages, exudates, and leakage of neovascular membranes after a mean follow-up of 7 months After external beam radiotherapy transient epiphora and ocular irritation was noted in 13 % of patients Although the results after a short period of follow-up are promising, well designed clinical trials remain necessary to evaluate whether radiation therapy is really an effective treatment for age-related subretinal neovascularisation and if there will be late treatment-associated morbidities

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CHAPTER 4

Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration. A pilot study

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ABSTRACT

Background: The natural course of the visual acuity (VA) of age-related subfoveal choroidal neovascularisation (CNV) membranes is poor Laser photocoagulation of subfoveal CNV is recommended if the patient is willing to accept a large decrease in VA immediately after treatment A large proportion of patients with subfoveal CNV do not meet the Macular Photocoagulation Study (MPS) Group guidelines for laser photocoagulation The fact that so few patients meet these criteria makes further research into new treatment techniques warranted Ionising radiation may prevent the proliferation of endothelial cells of newly formed subretinal capillaries and may induce obliteration of the aberrant new vessels

Methods: In this study, the effect of radiation therapy on subfoveal CNV membranes was evaluated Four groups of ten patients were treated with external beam radiotherapy (16 MV photons) on an area of 1 cm^2 (macular region) using a lens sparing technique and total dose of 8-24 Gy The first group received 8 Gy in one fraction The second, third and fourth groups received 12 Gy in 2 fractions, 18 Gy in three fractions and 24 Gy in four fractions, respectively The studied parameters included best-corrected VA and membrane size and leakage on the fluorescein angiogram (FA) We included 17 occult and 23 classic CNV membranes as defined by the MPS, with a duration of less than 5 weeks at presentation Complete ophthalmic examination including fluorescein angiography (FA) was performed before and 3, 12 and 18 months after radiation treatment We analysed the angiogram using a standard over-projection sheet The results concerning the VA and FA were compared with the extensively published natural course data

Results: The first group received 8 Gy in a single fraction In this group only four of ten patients had a stable visual acuity and stable FA appearance after 21 months of follow-up The VA and FA remained stable after 13 6 months of follow-up in seven of ten patients in group 2 (12 Gy) The third group (18 Gy) contained six patients with stable VA, although two of them, had CNV deterioration on the FA (11 1 months of follow-up) In the last group (24 Gy), with a short follow up of 5 6 months, eight patients had a stable VA and FA appearance We did not note any regression of the CNV on the angiogram The VA in groups 2,3 and 4

decreased to 0 1 or worse in only three cases, three cases and one case respectively after at least 6 months of follow-up

Conclusions: Comparison of these findings with the natural course data of subfoveal age-related CNV suggests a beneficial effect of radiation therapy with a total dose of 12 Gy or more on the progression of CNV To date no negative side effects have been observed

Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness in people over 50 years of age in Europe and the USA The prevalence of AMD increases with age, from 11 % of persons between 65 and 74 years to 27,9 % in those older than 75 years [4] AMD represents an age related change within the retinal pigment epithelium, photoreceptors and Bruch's membrane The decrease in phagocytosis of photoreceptor membranes leads to deposition of lipofuscin material (drusen) within Bruch's membrane [4] Secondary atrophy of pigment epithelial cells , overlying photoreceptor membranes and choriocapillaris results in the non-exudative stage (dry form) of AMD The exudative stage (wet form) develops when new choroidal vessels penetrate Bruch's membrane, resulting in choroidal neovascularisation (CNV) and serous pigment epithelial detachment (PED) [4]

Drusen which are hyperfluorescent (hydrophilic) on a fluorescein angiogram (FA) appear to predispose to the development of CNV The chemical composition of Bruch's membrane, the change in the pigment epithelium and the presence of macrophages which stimulate neovascularisation may all be relevant in the development of CNV [3] The exudative form of AMD has several clinical and angiographical manifestations

The classic CNV is a choroidal capillary proliferation through a break in Bruch's membrane characterised on the FA by a well-demarcated area of early hyperfluorescence and progressive leakage in the late stages Occult CNV is a subretinal pigment epithelial lesion that is presumed to be a CNV because of associated exudative or hemoorhagic manifestations, the effect of overlying pigment epithelium ot the vascular growth pattern [16,21] Although fibrovascular pigment epithelial detachments and late subretinal leakage of undetermined source are the common types of occult CNV according to the Macular Photocoagulation Study (MPS) Group [9,21] The natural course of the VA of classic CNV membranes is poor When the CNV is initially present within the foveal avascular zone the VA will be 20/200 or worse in approximately 70 % of the affected eyes within 18 months [4]

Laser photocoagulation of subfoveal CNV is recommended if the patient is willing to accept a large decrease in VA immediately after treatment On average, after 24 months, VA of laser treated eyes decreased three lines from baseline and visual acuity of untreated eyes decreased four lines [15] Although there is some beneficial effect of laser photocoagulation on subfoveal CNV membranes, there is still a considerable decrease in VA The challenge to reduce visual loss due to CNV has brought us to a concept in which we try to stop the growth of the neovascular membrane by the use of radiation therapy Ultrastructural examination of CNV has revealed that the cone was composed of a fibrovascular membrane characterised by endothelium-lined vascular channels with retinal pigment epithelium The rim of CNV was composed of fibrin, photoreceptor outer segments and macrophages [14] A CNV has been noted to grow at an average of 10 μm per day [13]

The treatment of CNV with ionising radiation is based on two hypothesis, ionising radiation may prevent the proliferation of endothelial cells necessary for neovascularisation and may induce the obliteration of aberrant vessels The effect of a single dose of 8 7 Gy on normal capillaries has been described by Reinhold [17] Within hours there is vasodilatation and swelling and vacuolation of the cytoplasm of endothelial cells A few weeks after irradiation loss of endothelial nuclei occurs with a reduction in the number and lenght of the capillaries and occlusive changes [7,17] The clinical effectiveness of ionising radiation (doses between 12 5 Gy and 20 Gy) on diffuse choroidal hemangiomas associated with serous retinal detachments has been demonstrated by Scott et al [18] In our opinion occlusive changes will occur in the newly formed subretinal vessels and the irradiation may prevent proliferation of endothelial cells of the aberrant new vessels The idea of using radiation for the treatment of newly formed retinal vessels in the eye is not new As early as 1948, a report was published of the complete collaps of newly formed retinal vessels in proliferative ocular disease (Eales' disease) after intensive roentgen therapy [12] The aim of the present study was to find a dose that would halt the proliferation of the CNV, yet entail little risk of cataract development. The most sensitive structure of the eye is the lens. The chance of cataract development is already 50 % after a dose of 5.5 Gy. The latency period, however, is 6.5 years after doses of 4-10 Gy [6]. We therefore developed a technique to avoid irradiation of the lens The oncogenic risk is about 0.25 %. It should be kept in mind that most of them will not live long enough to express any radiation-induced malignancy.

Materials and methods

The criteria for inclusion in the study were: (1) clinically and angiographically proven classic or occult subfoveal CNV associated with AMD, according to the MPS criteria [16,21]; (2) age older than 50 years; (3) informed consent.
Exclusion criteria were: (1) CNV associated with pathological myopia, angioid streaks and histoplasmosis: (2) previous photocoagulation of macular disease, (3) previous radiation therapy of eyes or brain. The study was performed with the permission of the local ethics committee for clinical experiments.

The study population consisted of 40 patients with angiographically proven classic and occult subfoveal CNV membranes associated with AMD. For a rejection error of 5 % and a therapeutic effectiveness of 30 %, groups should contain 10 patients [18]. The patients were divided into the following four treatment groups. Group 1. ten patients received 8 Gy in one fraction. Group 2: ten patients received 12 Gy in two 6 Gy fractions. Group 3: ten patients received 18 Gy in three 6 Gy fractions. Group 4: ten patients received 24 Gy in four 6 Gy fractions. The interval between fractions was 1 week. We used 16-MV photons on an area of 1 cm^2 with a lens-sparing technique. 16-MV photons were chosen because with high-energy photons the dose administered at the surface of the eye is relatively low. To reduce the lens dose the beams were directed 30 degrees from the optical axis in the cranial/caudal direction. With this technique the lens dose is less than 30 % of the total dose (Figure 1). The radiation fields cross each other in the macular region. Outside the macular area the dose decreased to 50 % or less of the total dose. Patients were asked to look at a fixed point during irradiation.

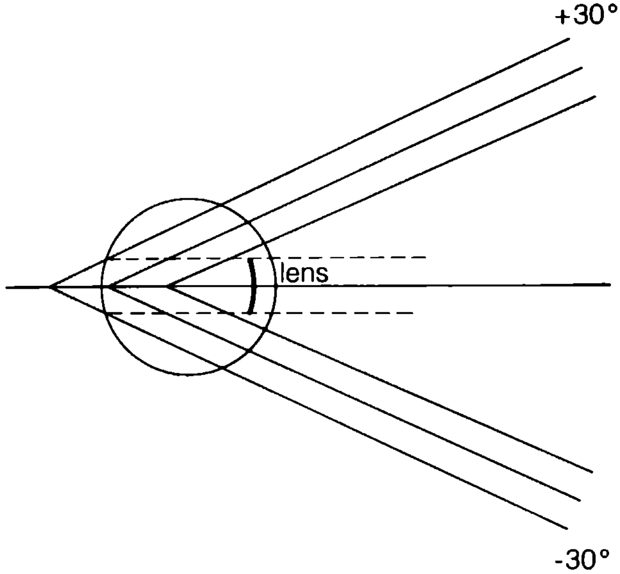

Figure 1 *Lens-sparing technique The radiation beams are directed 30° from the optical axis*

All patients had a recent history of acute decrease in VA and were submitted for radiation therapy within 5 weeks after the beginning of the VA drop After a complete ophthalmic examination including FA, best corrected visual acuity for distance and Amsler test, the patients were asked to participate in this pilot study There were no refusals All patients underwent ophthalmic examination 1 day, 4 weeks, 3, 6, 12, 18 months after radiation therapy FA and colour photography were repeated 3, 12 and 18 months after radiation therapy The initial FA was usually performed within 10 days before the start of radiation therapy, although in seven patients there was a longer interval

The early, mid-venous and late phases of the pre- and posttreatment angiograms were analysed using an over-projection sheet for measuring the size of the membrane and the leakage of fluorescein in the late phase When there was an increase in size of the CNV in the early phase and/or an increase in late phase leakage the CNV was considered to be progressive When no change between the pre- and posttreatment angiograms was seen, CNV was noted as stable The interpretation of occult CNV development was more difficult because of the overlying PED and/or the obscuring blood Some of the occult CNV had a classic component which could be interpreted, others had leakage from an undetermined source which could be evaluated by comparing the pre- and post-treatment leakage When the overlying blood disappeared after a few months and the extension of the lesion using an over-projection sheet did not increase, we classified the lesion as stable on FA A decrease in VA was defined as a drop of two or more lines of the Snellen test Stable VA was defined as an increase or decrease within two lines from initial best-corrected VA A two-line drop of VA in our test is comparable to a three-line drop in the data used in the MPS study on subfoveal CNV [15]

RESULTS

The initial (baseline) FA showed in 23 patients a classic CNV membrane and in 17 patients an occult membrane as defined by the MPS [15] In a recent article the presenting clinical findings were evaluated concerning the neovascular form of AMD [10] About 87 % of the presenting patients had occult CNV, with 84 % having subfoveal disease [10] It is difficult to include only classic CNV, because of the high number of cases of occult CNV

Group 1 In the first group (8 Gy in one fraction, Table 1) the mean follow-up was 21 months (range17-24 months) The average age was 77 8 years (range 74-87 years) In six patients there was a decrease in VA to 0 1 or worse after radiation treatment The VA drop occurred in all patients within 3 months after treatment In the other four patients the VA remained stable with no deterioration of the CNV membrane on the FA Only one of three occult CNV membranes remained stable

Table 1 *Radiation therapy. 8 Gy in 1 fraction (group 1)*

case	age/ gender	VA inclusion	VA final	follow-up (months)	FAG	CNV type
1	74/F	0 25	0 3	22	stable	classic
2	76/M	0 3	0 1	17	worse	classic
3	74/M	0 16	1/60	18	worse	occult
4	82/F	0 1	0 25	22	stable	classic
5	74/M	0 2	2/60	22	worse	classic
6	87/M	0 3	0 3	24	stable	classic
7	74/M	0 3	0 2	22	stable	occult
8	77/M	0 4	0 1	19	worse	occult
9	77/F	0 3	1/60	21	worse	classic
10	83/M	0 2	0 08	23	worse	classic

Table 2. *Radiation therapy. 12 Gy in 2 fractions of 6 Gy (group 2)*

case	age/ gender	VA inclusion	VA final	follow-up (months)	FAG	CNV type
1	85/F	0 3	2/60	13	worse	classic
2	79/M	0 3	0 25	11	stable	classic
3	77/M	0 25	0 3	12	stable	classic
4	80/M	0 3	0 3	15	stable	occult
5	69/F	1/60	1/60	15	stable	classic
6	69/F	0 16	0 2	14	stable	classic
7	90/F	0 16	0 08	14	worse	occult
8	58/F	0 5	0 4	14	worse	occult
9	82/F	0 125	2/60	13	worse	occult
10	84/F	3/60	1/60	15	stable	classic

Group 2 The mean follow-up in the second group (12 Gy in two fractions, Table 2) was 13 6 months (range 11-17 months) and the average age was 77 3 years (range 58-90 years) There was stable VA in seven patients, although one patient (no 8) had signs of deterioration on the FA Only one of four (no 4) occult membranes remained stable concerning the VA and the FA apperance, the other three had a decrease in VA to 0 1 or worse

Group 3 The third group (18 Gy in three fractions, Table 3) with a mean follow-up of 11 1 months (range 8-14 months) and an average age of 76,9 years (range 68-84 years), contained only three classic membranes Four patients had a decrease in VA (three with a VA of 0 1 or worse) after radiation therapy and they all had an initial occult CNV In five patients the VA remained stable, with in three patients no change in FA appearance In two patients (nos 5,9) FA deterioration occurred Patient no 1 had an increase in VA because of the dissappearance of subretinal fluid associated with the CNV

Table 3. *Radiation therapy 18 Gy in 3 fractions of 6 Gy (group 3)*

case	age/ gender	VA inclusion	VA final	follow up (months)	FAG	CNV type
1	72/M	1/60	0 2	10	stable	classic
2	82/M	0 3	0 25	12	stable	classic
3	80/F	0 25	1/60	8	worse	occult
4	84/F	0 2	1/60	14	worse	occult
5	71/F	0 25	0 25	14	worse	occult
6	79/F	0 3	0 25	14	stable	occult
7	75/F	0 25	0 08	10	worse	occult
8	76/F	0 3	0 3	9	stable	occult
9	68/M	0 2	0 25	9	worse	classic
10	82/F	0 3	0 16	11	worse	occult

Group 4. The mean follow-up in the fourth group (24 Gy in four fractions; Table 4) was 5.6 months (range 4-7 months) and the average age was 74.3 years (range 69-83 years). Only one patient had a decrease in VA according to our definition, but patient no. 6 had a slight decrease in VA associated with a deterioration on the FA. The other eight patients, including two occult CNV membranes (nos. 2,7), had stable VA and FA appearance.

Table 4. *Radiation therapy. 24 Gy in 4 fractions of 6 Gy (group 4)*

case	age/ gender	VA inclusion	VA final	follow-up (months)	FAG	CNV type
1	70/M	0.3	0 25	6	stable	classic
2	69/F	0.2	0 2	6	stable	occult
3	78/F	0 08	1/60	7	worse	occult
4	72/F	0 25	0 25	6	stable	classic
5	81/F	0 2	0 2	4	stable	classic
6	70/M	0 2	0 1	7	worse	classic
7	83/M	0 16	0 16	4	stable	occult
8	74/M	0 5	0 5	6	stable	classic
9	75/M	0 16	0 125	5	stable	classic
10	71/M	0.4	0 3	5	stable	classic

In group 1, a decrease in VA and an FA deterioration occurred in six patients. Only four patients had a stable VA and FA after therapy (21 months follow-up). In three patients of group 2 the VA and FA deteriorated, and in seven patients there was a stable situation (13.6 months follow-up). The third group, with seven initial occult CNV membranes, had six patients with stable VA after treatment but two of them showed FA deterioration (11 1 months follow-up). In group 4, stable post-irradiation VA and FA occurred in eight patients, but with a relatively short follow-up (5.6 months) Except for the two patients (nos.5,9) in group 3, all the patients with a stable VA had a CNV membrane that remained unchanged on FA appearance after radiation therapy (Figure 2). None of the patients showed CNV membrane regression on FA appearance If a drop in VA or a deterioration on the angiogram was noticed, it occurred within 3 months after treatment (Figure 3) None of the patients noticed any side effect of this therapy Complications such as radiation keratitis or radiation retinopathy were not encountered Slight changes in lens opacification could not be ruled out, but we did not notice a substantial progression of cataract in our patients We are aware of the fact that the follow-up is still short and that some side-effects become apparent only after several months or years

Discussion

The prevalence of AMD in a general population over the age of 65 years is about 25 % Although only 12 % of patients with AMD have the exudative stage, they constitute 88 % of those who become legally blind [8] No control group was included in this study because the natural course of subfoveal membranes is well documented [3,5,11,19] The natural course of classic CNV membranes in AMD has been described by Bressler et al [3] A subfoveal CNV, with an initial VA of 0 1 or better, shows in at least 70 % of the eyes a VA of 0 1 or worse after 21 months of follow-up Guyer et al found that 77 % of eyes with a subfoveal CNV had lost at least four lines of VA after 24 months follow-up [10] The natural course of occult CNV membranes with an initial VA of 0 25 shows a decline of at least three lines in 63 % of patients after 28 months of follow-up [5] The natural course of a PED with a CNV is even worse Some 86 % of patients with an initial VA better than 0 2 and a subfoveal CNV associated with a PED had a final VA of 0 1 or worse after 48 months follow-up [20]

The MPS recommends laser photocoagulation for classic subfoveal CNV membranes if the patient is willing to accept a large decrease in VA immediately after treatment In the long term, treated patients had less decrease in VA from baseline Persistent or recurrent CNV was observed in 51 % of the laser treated eyes by 24 months after initial treatment [14] Perifoveal laser photocoagulation has also been proven to be effective in the short term preservation of VA, but this treatment led to a six line VA loss after 42 months in 76 % of patients [8] Compared with eyes in natural history studies, eyes treated with unconventional scatter macula photocoagulation had less visual loss from baseline but did not recover VA of 0.2 or better more frequently [21]. Except for the limited benefit of laser photocoagulation there is no therapeutic modality for patients with CNV membranes.

In 1992 we reported the preliminary results of this study [2]. Chakravarthy et al. recently reported a beneficial effect of teletherapy with 6-MV photons (doses 10-15 Gy in five fractions) on subfoveal CNV [7]. VA was maintained or improvred in 78 % and 63 % of the patients at their 6- and 12 months follow-up examination, respectively. Significant CNV regression was recorded in 68 % and 77 % of treated patients at 6 and 12 months after irradiation. No differences were seen between patients who received 10 Gy and those who received 15 Gy. The vaso-occlusive response became obvious at 6 months after irradiation [7]. The present work showed that a single fraction of 8 Gy had no beneficial effect Only four of ten patients had stable VA and FA appearance after 21 months, which is comparable with the natural history of subfoveal CNV membranes. In the second group (12 Gy in two fractions) and the third group (18 Gy in three fractions), VA remained stable for at least 12 months in seven and six cases, respectively. These results are comparable with the outcome of the study by Chakravarthy et al. [7] In contrast with their angiographically proven CNV regression we could note only inhibition of the expansion of the CNV membranes in the majority of our patients with stable VA. Two patients (nos. 5,9) of the third group had FA deterioration but stable VA. These patients had a period of 4 weeks between the baseline FA and the first radiation treatment Compared with the other groups, the fourth group (24 Gy in four fractions) had only a short follow-up (5.6 months), but it is promising that eight of ten patients had a stable VA and FA appearance

The differences in angiographic outcome between the two studies may be due to differences in treatment volume. In the present study only 1 square cm of the choroid was irradiated, while Chakravarthy et al. treated more than 50 % of the choroid. Other reasons for differences in post-treatment changes in FA appearance are a delay of more than 10 days between the initial angiogram and initiation of treatment (group 2, nos.7,8,9; group 3, nos. 3,5,9; group 4, no.6) and a larger percentage of occult membranes in the present study. The presence of an occult CNV membrane (17/40 patients) sometimes made it difficult to compare the initial and final FA. It should be noted that in contrast to the study by Chakravarthy et al., in which only four of the 19 patients had an initial VA of 6/24 or more, in our study 22 of the 40 patients presented with initial VA of 25/100 or more We also excluded patients with previous laser treatment, whereas the other study contained five patients with previous laser treatment in the macular region

To date we have seen no side effects of radiation therapy According to the literature the lens is the most sensitive part of the eye for radiation damage [1,6,17] With the lens-sparing technique we used, the expected lens dose is less than 30 % of the total dose In group 3 (18 Gy) and group 4 (24 Gy), with lens doses of 6 Gy and 8 Gy, respectively, there remains a possibility of cataract development

In conclusion, stable VA was observed in six to eight of the ten patients in each of the groups 2,3 and 4 (12 Gy, 18 Gy and 24 Gy), associated with a stable CNV membrane on FA in all except two cases The MPS data show that the VA of eyes with untreated subfoveal CNV with an initial VA of 0 1 or better will decrease to 0 1 or worse in 44 % of eyes within 3 months of follow-up [15] The VA in our groups 2, 3 and 4 decreased to 0 1 or worse in three,three and one patient, respectively, after at least 6 months of follow-up Although the follow-up is still short (especially in group 4), patients treated with total doses of 12 Gy or more seem to do better than one might expect from the natural history of this disease To date no negative side effects have been observed Longer observations will show whether the proposed treatment is indeed safe The positive results of the present study, however, warrant further investigation to determine the role of radiation therapy in the treatment of CNV membranes

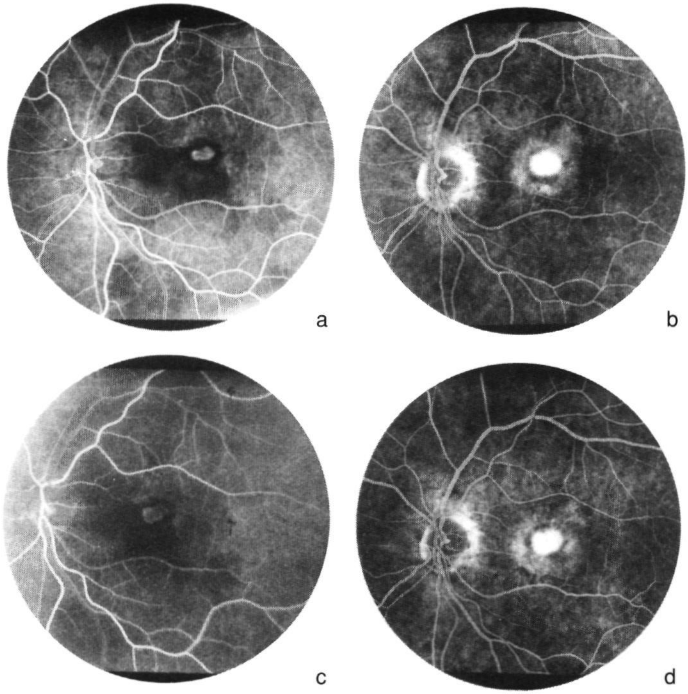

Figure 2. *Patient 2 (12 Gy group). Visual acuity in left eye 0.3 before treatment and 0.25 after treatment (follow-up 12 months).* ***2a****, Early phase before treatment.* ***2b****, Late phase before treatment.* ***2c****, Early phase 12 months after treatment.* ***2d,*** *Late phase 12 months after treatment.*

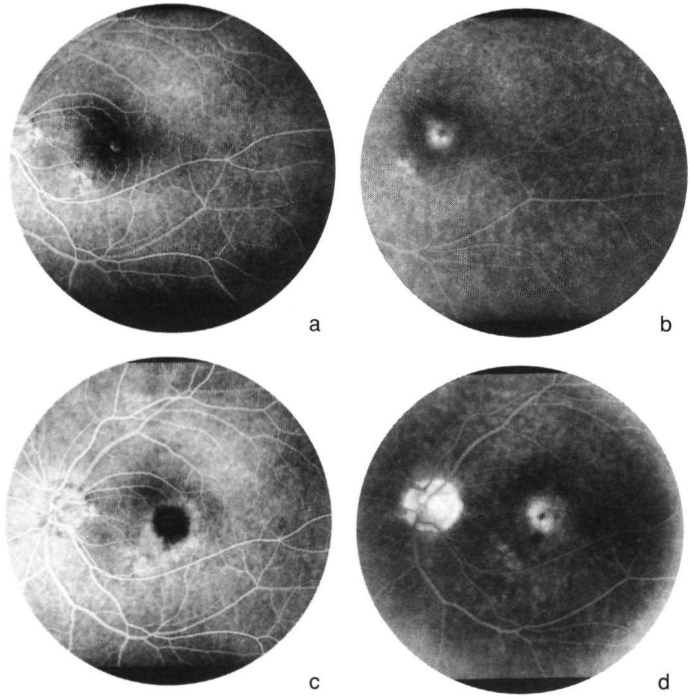

Figure 3. *Patient 9 (18 Gy group). Visual acuity in left eye 0.2 before treatment and 0.25 after treatment (follow-up 9 months).* ***3a****, Early phase before treatment.* ***3b****, Late phase before treatment.* ***3c****, Early phase 3 months after treatment.* ***3d****, Late phase 3 months after treatment.*

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CHAPTER 5

Radiation therapy for age-related subfoveal choroidal neovascular membranes. A pilot study

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ABSTRACT

In this pilot study the effect of radiation therapy on subfoveal CNV membranes associated with AMD was evaluated Four groups of 10 patients were treated with external beam radiotherapy (16 MV photons) on an area of 1 cm^2 (macular region) using a lens-sparing technique and a total dose of 8 to 24 Gy The first group received 8 Gy in a single fraction In this group only 30 % had a stable visual acuity and a stable FA after 18 months of follow-up In 50 % of patients in group 2 (12 Gy) and 40 % of patients in group 3 (18 Gy) the visual acuity (VA) and FA appearance remained stable after 18 months of follow-up In the last group (24 Gy) 80 % of patients had a stable VA and FA appearance after 12 months follow-up Comparison of these findings with the natural history data of subfoveal age-related CNV, suggests a beneficial effect of radiation therapy with a total dose of 12 Gy or more on the progression of CNV membranes

Introduction

AMD is a leading cause of blindness in people over 50 years in Europe and the USA The prevalence of AMD increases with age to 25 % in those older than 65 years [1] Although only 12 % of patients with AMD have the exudative stage with the development of a CNV, they constitute 88 % of those who become legally blind [2] The indications for laser treatment of subfoveal CNV have been well defined by the Macular Photocoagulation Study (MPS) group But a recent article by Yannuzzi et al suggests that a large proportion (87%) of patients with neovascular AMD do not meet the MPS guidelines for laser treatment Because so few patients meet these criteria, further research into new techniques for treatment of this disorder is warranted [3]

The natural course of th VA of subfoveal CNV membranes is poor When a CNV is initially present within the foveal avascular zone the VA will be 20/200 or worse in approximately 70 % of the affected eyes within 18 months [1] The treatment of CNV with ionising radiation is based on the hypothesis that ionising radiation may prevent the proliferation of endothelial cells necessary for neovascularisation and may induce the obliteration of aberrant vessels [4] The most sensitive structure of the eye concerning irradiation is the lens The latency time between the radiation treatment and the development of cataract after a total dose of 4 to 10 Gy will be 6 5 years on average [5]

Materials and methods

We included 40 patients with an angiographically proven classic or occult subfoveal CNV associated with AMD and a VA of 0 1 or better at presentation This study was performed with permission of the institutional ethical committee for clinical experiments The first group of 10 patients (mean age 77 years) received 8 Gy in 1 fraction The second group (mean age 77 years) received 12 Gy in 2 fractions The third group (mean age 76 years) and the fourth group (mean age 74 years) received 18 Gy in 3 fractions and 24 Gy in 4 fractions respectively The baseline FA showed in 23 patients a classic CNV membrane and in 17 patients an occult CNV membrane as defined by the MPS [6,7] Most patients had a recent history of acute decrease in VA based on subfoveal CNV, and were treated within 5 weeks after the beginning of the drop in VA All patients underwent a complete ophthalmic examination including fluorescein angiography before treatment and 3, 12 and 18 months post-treatment

The early, mid venous and late phase of the pre- and post-treatment angiograms were analysed using an over-projection sheet for measuring the size of the membrane and the leakage of fluorescein in the late phase When there was an increase in size of the CNV in the early phase and/or an increase in late phase leakage the CNV membrane was considered to be progressive When no change between the pre and post-treatment angiograms was seen, the CNV was noted as stable A decrease in VA was defined as a drop of 2 or more lines at the Snellen test A stable VA was defined as an increase or decrease within 2 lines from initial best corrected VA We used 16 MV photons on an area of 1 cm^2 with a lens sparing technnique

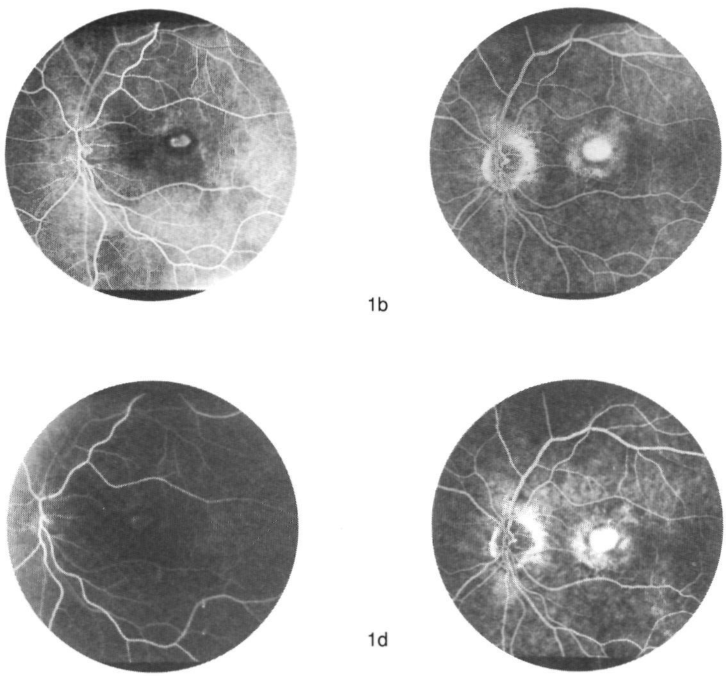
Results

In the first group (n=10,8 Gy), only 3 patients had a stable VA and FA after 18 months of follow-up The drop in VA occurred in 6 patients within 6 months after treatment The second group (n=10, 12 Gy) contained 7 patients with a stable VA and FA after 12 months of follow-up, but in two patients a deterioration occurred 12 months after treatment The third group (n=10, 18 Gy), with 7 occult CNV membranes, showed in 4 patients a stable VA and FA after 18 months of follow-up After 12 months of follow-up there were 6 stable patients Only 2 patients in the fourth group (n=10, 24 Gy) had a decrease in VA and a FA deterioration after 12 months of follow-up The other 8 patients were all stable after one year The results are summarised in Table 1

Table 1. *Number of patients with a stable visual acuity (VA) and a stable fluorescein angiogram (FA) after radiation treatment*

Group (n=10)	No classic No occult total	follow-up 6 months	follow-up 12 months	follow-up 18 months
Group 1 8 Gy	7 classic 3 occult 10 total	3 1 4	2 1 3	2 1 3
Group 2 12 Gy	6 classic 4 occult 10 total	6 1 7	6 1 7	4 1 5
Group 3 18 GY	3 classic 7 occult 10 total	3 3 6	3 3 6	2 2 4
Group 4 24 Gy	7 classic 3 occult 10 total	6 2 8	6 2 8	? ? ?

After 12 months of follow-up 60-80 % of patients in group 2, 3 and 4 show a stable VA and FA appearance, but after this period 2 eyes in group 2 and 3 deteriorated. None of these patients noticed any side effect of this therapy. Complications such as radiation keratitis were not encountered. Slight changes in lensopacification could not be ruled out, but we did not notice a substancial progression of cataract in our patients.



1a 1b

1c 1d

Figure 1. *Case study. Male patient, left eye, visual acuity 0.3, 12 Gy group.* ***1a****, Early phase before treatment.* ***1b****, Late phase before treatment.* ***1c****, Early phase one year after treatment.* ***1d****, Late phase one year after treatment.*

Discussion

In this study a control group was not included because there is well documented information about the natural course of subfoveal CNV membranes [1,8,9,10] The natural course of classic CNV membranes has been described by Bressler et al A subfoveal CNV, with an initial VA of 0 1 or better, shows in at least 70 % of the eyes a VA of 0 1 or worse after 18 months of follow-up [1,9] The natural course of occult CNV is even worse [11] The MPS Group compared the VA after laserphotocoagulation of subfoveal CNV with the natural course findings of subfoveal CNV [6,7] The VA of eyes with untreated subfoveal CNV with an initial VA of 0 1 or better, will decrease to 0 1 or worse in 44 % of eyes after 3 months follow-up and in 80 5 % of eyes after 24 months of follow-up [6] Laserphotocoagulation of subfoveal CNV has some beneficial effect, but the patient must be prepared for a large decrease in visual acuity immediately after treatment [6] After 18 months follow-up 7 patients in the 8 Gy group had a VA of 0 1 or worse, which is comparable to the natural course data In the 12 Gy and 18 Gy group, 3 and 4 patients respectively had a VA of 0 1 or worse after 12 months, but in both groups 2 other patients had a drop in VA within 18 months of follow up Although the follow up in the 24 Gy group is not exceeding 12 months, 8 out of 10 patients remained stable, and only 2 patients had a decrease in VA to 0 1 or worse When compared to the natural history data (44 % of eyes develop a VA of 0 1 or worse within 3 months), the patients treated with 12,18 and 24 Gy show less loss of VA (20-40 % a VA of 0 1 or wores within 12 months) There is a possibility that the radiation treatment has decreased or stopped the growth speed of the neovascular membrane

A Belfast study group reported a beneficial effect of teletherapy, with 6 MV photons and total doses of 10-15 Gy in 5 fractions on subfoveal CNV After 12 months follow-up the VA was maintained or improved in 63 % of patients and they noticed a CNV regression in 77 % of patients on the angiogram [12] Their results concerning the VA are comparable with the results of the 12, 18 and 24 Gy group after 12 months of follow-up In contrast to their angiographically proven CNV regression we could only note an inhibition of the expansion of the CNV membrane after irrsdiation The differences in angiographical outcome may be due to differences in treatment volume In the present study only 1 cm^2 of the choroid received a total dose, while the whole choroid of the eye in the Belfast study was treated with the total dose The presence of occult CNV (43 % of eyes) made it sometimes difficult to compare the initial and final FA appearance in our pilot study

In conclusion, after 12 months of follow up patients treated with 12 and 18 Gy total dose, show more patients with a VA of 0 1 or better than you might have expected from the natural course The 24 Gy group, with 8 stable patients after 12 months, shows promising results Although the follow up is still short, the patients treated with low doses of irradiation seem to do better than one might expect from the natural history data Until now there are no negative side effects, but longer observation is needed for a definite answer The results of the Belfast study and this pilot study warrant further investigation to determine the role of radiation treatment of CNV membranes, knowing that cumulative doses of radiation up to 25 Gy causes no observable damage to the neuroretina and optic nerve [4] The final answer has to come from a randomized study including a control group of patients

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CHAPTER 6

Visual acuity and scar size in eyes with age-related subfoveal choroidal neovascular lesions, 30 months after radiation therapy.

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ABSTRACT

Purpose and methods: In a pilot study to determine the effectiveness of ionizing radiation on the deterioration of subfoveal choroidal neovascularisation (CNV), the affected eyes of 10 patients were treated with a total dose of 24 Gy (6 Gy fractions) A special lens-sparing technique was used to avoid cataract development During 30 months of follow-up the visual acuity (VA) and scar size (SS) of the treated eyes of all 10 patients were evaluated The ten fellow eyes included four eyes with untreated age related disciform scarring already present at inclusion

Results: After 30 months of follow-up 5 treated eyes showed a stable VA and fluorescein angiogram (FA) appearance The other 5 eyes had progressive disease We were able to compare 4 eyes with progressive disease after radiation treatment, with 4 fellow eyes with untreated age related disciform lesions already present at inclusion The 4 eyes treated with radiation therapy had better VA and smaller SS, 30 months after inclusion, compared with the untreated fellow eyes with a stable disciform scar

Conclusions: The results suggest that radiation with 24 Gy either stabilizes or delays the deleterious effects of CNV on the visual acuity and scar size Until now no late side effects have been observed

Introduction

The exudative form of age-related macular degeneration (AMD), with the development of choroidal neovascularisation (CNV), is a leading cause of blindness in western countries The effect of laser photocoagulation for selected cases of subfoveal CNV is well known from the macular photocoagulation study (MPS) investigations [1,2,3,4] The patient must accept an immediate and permanent decrease of VA after laser photocoagulation, but will have better VA using low-vision aids [1,2,3] Only in case of a small CNV with a moderate or poor

VA foveal ablation is recommended [4]. Other modalities of laserphotocoagulation including foveal sparing techniques are being proposed as alternative treatments but their definitive value has not been proved [5] Only a few patients with recent subfoveal CNV are suitable for laser therapy, because a large proportion (87 %) of patients have an occult or poorly-defined CNV at presentation [6]. Alternative forms of therapy for CNV are proposed, like submacular surgery, Interferon therapy, ICG-guided laser therapy and Thalidomide therapy but none of these new therapies seems to be valuable [7]. Patients with unilateral age-related exudative maculopathy developed neovascular membranes in the fellow eye in 31 % of cases after 4 years of follow-up, and in general patients with exudative disease in one eye develop CNV in the fellow eye at a rate of about 5-10 % per year [8].

The hypothesis that ionizing radiation may prevent endothelial cell proliferation and/or induce aberrant vessel obliteration and influences macrophages depended growth factors and/or regulatory genes, in case of CNV, is under investigation [7]. After the first report concerning the effect of radiation therapy on subfoveal CNV in 1992, several other reports were published [9,10,11,12,13,14]. We are now able to present the results after 30 months of follow-up concerning ten patients treated with radiation therapy with a total dose of 24 Gy (6 Gy fractions). We decided to do a longer follow-up in this group of patients because initially they showed the best results after 12 months post-irradiation in our pilot study [11,13].

Materials and methods

This study was performed with permission of the institutional ethical committee for clinical experiments. The early results of this group of patients were previously published [11,13]. Ten patients with subfoveal CNV and recent decrease of VA were treated with a total dose of 24 Gy in 4 fractions of 6 Gy in the macular area. The time between two consecutive fractions was 1 week and the overall treatment time was 3 weeks. The dose was delivered by two 1 cm^2 16 MV photon beams. The two photon beams diverge 30 degree from the eye axis and cross the eye axis in the macular area. By this technique the lens will receive less than 30 % of the total dose All patients underwent a complete ophthalmic examination of both eyes, including FA, before treatment and 3, 12, 18 and 30 months post treatment The early, mid and late venous phase of the pre- and post-treatment angiograms were analysed using an over-projection sheet for measuring the size of the membrane (disc areas=DA) and the leakage of fluorescein in the late phase When there was an increase in size of the CNV in the early phase and/or an increase in late phase leakage the CNV membrane was considered to be progressive When no change between the pre- and post-treatment angiograms was seen, the CNV was considered as stable Any CNV with a classic component but partial occult (including subretinal blood and/or fluid or late undetermined leakage) was classified as occult type of CNV A decrease in VA was defined as a drop of 2 or more lines at the Snellen test A stable VA was defined as an increase or decrease within 2 lines from initial best corrected VA After 30 months of follow-up the VA and FA of the treated eyes and fellow eyes of all 10 patients were documented

Results

The patients treated with a total dose of 24 Gy (6 Gy fractions) showed the following characteristics (Table 1 and Table 2)

Patient 1 Male, 72 years

He presented with a classic type of CNV in the right eye and an initial VA of 0 3 (Figure 1, before treatment, **left**) After 30 months of follow-up the VA was 0 2 and the central SS was 1 DD (Figure 1, after treatment, **right**) His fellow left eye showed drusen and a VA of 1 0

Patient 2 Female, 71 years

This patient initially had a VA of 0 2 and an occult type of CNV After 30 months the VA dropped one line to 0 1 and the FA appearance of the CNV remained stable with a scar size of 2 DD Her fellow eye with a scar of 2 DD had a VA of 0 4

Patient 3 Female, 80 years

This patient showed a drop in VA from 0 08 to 1/60 within 3 months after radiation therapy for occult CNV After 30 months of follow up her VA in the study eye is 1/60 with a SS of 6 DD Her fellow eye already had disciform scarring for more than one year without laser treatment at presentation, with a SS of 12 DD After 30 months of follow up the SS in the fellow eye stabilized and the VA remained 2/300

Patient 4 Female, 74 years

This patient presented with a classic CNV (OD) and an initial VA of 0 25 (Figure 2, OD before treatment, **left**) A drop in VA occurred after 18 months post-radiation treatment and she ended up with a VA of 0 1 and a SS of 2 DD after 30 months (Figure 2, OD after treatment, **right**) The fellow left eye showed untreated disciform scarring present for more than one year at presentation and with a stable SS of 6 DD and a VA of 2/60 after 30 months of follow up (Figure 3)

Patient 5 Female, 83 years

The left eye with a classic CNV and an initial VA of 0 2 showed a stable angiogram with a SS of 2 DD after 30 months The VA decreased to 0 125 after 30 months post-treatment The fellow eye has a VA of 0 8 and drusen in the macular area

Patient 6 Male, 72 years

This patient presented with a classic CNV with an initial VA of 0 2 A decrease in VA to 0 1 after 6 months and to 1/60 after 12 months post-treatment occurred The SS of 1 DD at presentation enlarged to 4 DD at 30 months of follow-up The fellow right eye still has a VA of 0 8 and has some pigmentary changes in the macular area

Patient 7 Male, 85 years

Between 12 and 18 months after treatment for occult CNV, the VA declined from 0 16 to 2/60 and after 30 months the VA is 2/60 with a SS of 5 DD The fellow eye with a VA of 1/60 had disciform scarring, without previous laser treatment, at presentation with a SS of 6 DD

Patient 8: Male 76 years.

The left eye with classic CNV and an initial VA of 0.5 showed a decrease in VA to 0.2 after 12 months and to 0.08 after 30 months of follow-up with an increase in SS from 1 DD to 3 DD. The fellow eye with a VA of 1/60 and a scar size of 4 DD at presentation remained stable during 30 months of follow-up. This eye was not treated with laserphotocoagulation.

Patient 9: Male 77 years.

The right eye presented with a classic CNV and a VA of 0.16. At the end of the follow-up period the VA increased to 0.25 and the FA remained stable. The fellow eye with some drusen had a stable VA of 0.8.

Patient 10: Female 73 years.

This patient with a classic CNV had a stable VA of 0.3 during the follow-up period, with a SS size of 1 DD. The fellow eye with a VA of 0 8 did not show any change.

Table 1. *Patients (n=5) with stable visual acuity (VA) and scar size (SS) on fluorescein angiography 30 months after radiation therapy with a total dose of 24 Gy (6 Gy fractions) compared with the untreated fellow eye.*

Patient No	Study eye VA	Study eye SS	Fellow eye VA	Fellow eye SS
1.	0.2	1 DA	1.0	drusen
2.	0.1	2 DA	0.4	2 DD
5	0.125	2 DA	0.8	drusen
9.	0.25	2 DA	0 8	drusen
10.	0.3	1 DA	0 8	drusen

Table 2 *Patients (n=5) with deterioration of visual acuity (VA) and scar size (SS) on fluorescein angiography 30 months after radiation therapy with a total dose of 24 Gy (6 Gy fractions) compared with the untreated fellow eye*

Patient No	Study eye VA	Study eye SS	Fellow eye VA	Fellow eye SS
3	1/60	6 DA	2/300	12 DD
4	0 1	2 DA	3/60	6 DD
6	1/60	4 DA	0 8	drusen
7	2/60	5 DA	1/60	6 DD
8	0 08	3 DA	1/60	4 DD

Thirty months after radiotherapy, with a total dose of 24 Gy, 5 out of 10 patients have a stable VA without progression of the CNV on FA (Table 1) Patient 1 5, 9 and 10 presented with a classic CNV, while patient 2 had an occult CNV The VA initially was better than 0 1 and remained stable in all cases at 30 months after radiotherapy The other 5 patients had progressive disease with a decrease in VA and an increase in SS despite radiation therapy (Table 2) Patient 3, 6 and 7 ended up with a VA of finger counting at 1 or 2 meter, while patient 4 and 6 had a VA of 0 1 and 0 08 respectively after 30 months Four (patient 3,4,7,8) of the the 5 patients with progressive disease, had untreated disciform scarring in the fellow eye at presentation The 4 eyes treated with radiation therapy had better VA and smaller SS compared with the untreated fellow eyes after 30 months of follow-up (Table 2) Until now we did not see any severe side-effects of this radiation therapy such as radiation retinopathy or dry eyes Slight changes in lensopacification, however, can not be ruled out

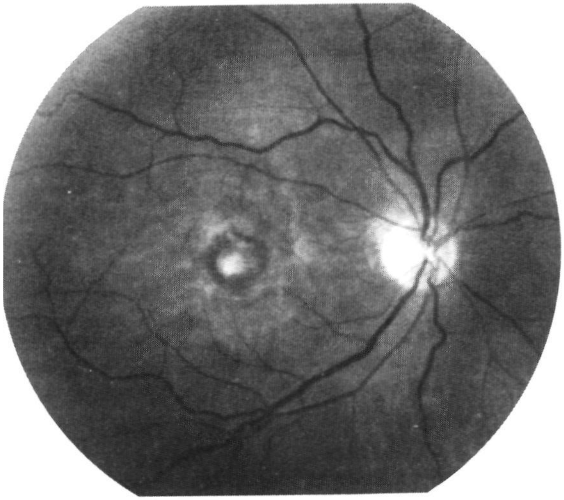
Discussion

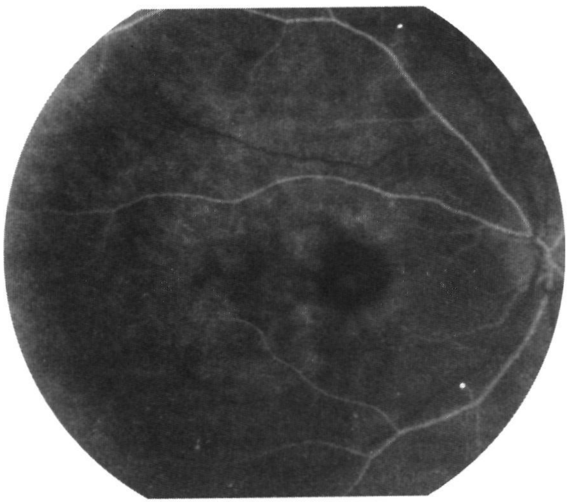
In exudative AMD new capillaries proliferate under the retinal pigment epithelium and/or between the retinal pigment epithelium and the retina after they have broken through Bruch's membrane They leak blood, lipoproteins and subretinal fluid in the active phase Over a period of months fibrous tissue appaers with the development of a fibrovascular disciform scar, with secundary destruction of the overlying photoreceptors and the remaining retinal pigment epithelium

According to Bird there are no well formulated concepts concerning the mechanism by which neovascularisation is induced Maybe macrophages cause vasoproliferation by producing growth factors [15] Finger et al concluded after reviewing the literature that possibly radiotherapy indirectly effect genes resulting in growth arrest and/or apoptosis [14] The Belfast study group postulated that radiotherapy acts to minimise size and intensity of the disciform response, through arresting the proliferation of endothelial cells resulting in mitotic cell death and through its attenuating effects on the inflammatory response resulting in a reduced disciform scar [12] Their results concerning radiotherapy for exudative AMD are encouraging, because the VA was significantly better and the SS was smaller in 11 eyes treated with radiotherapy, compared with the untreated fellow eyes with disciform scarring after a mean follow-up of 28 months After reviewing the literature they concluded that concordance in scar size between the eyes of untreated patients was found to be highest when the duration of the disease was at least 12 months in the second eye to be affected This implies that the appearance of the fibrovascular disciform scar does not change substantially after 12 months from initial presentation [12]

The natural course of the visual acuity in patients with classic or occult CNV is known from many studies [1,2,3,4] The VA of eyes with untreated subfoveal CNV with an initial VA of 0 1 or better, will decrease to 0 08 or worse in 44 % of eyes after 3 months of follow-up and in 80 5 % of eyes after 24 months of follow-up When compared to the natural course of the disease (80 5 % of eyes deteriorate to a VA of 0 08 or worse within 24 months) radiation the dose of 24 Gy seems to have a beneficial effect on the VA (3 of 10 eyes had a VA of 0 08 or worse within 30 months) Although 5 eyes showed progresssive disease after radiation therapy, we noticed in 4 of them a better VA and smaller SS after 30 months, when compared with the untreated fellow eyes with exudative AMD These results confirm the results of the Belfast study group [12] Radiation may have some negative side effects on the eye when doses are given beyond tolerance levels The lens is a relatively radiosensitive structure and opacification will develop when doses exceed 6-12 Gy In this study the radiation was applied in such a way that the lens was more or less spared Until now there are no indications that there is an increased incidence of cataract in the treated eyes More severe side-effects such as radiation retinopathy or radiation optic neuropathy are rare after doses of 46 5 Gy and 55 Gy (2 0 Gy fractions) respectively [16] Four fractions of 6 Gy, given in 3 weeks, is more or less biologically equivalent to 50 Gy given in 25 daily fractions of 2 Gy The incidence of radiation damage after 24 Gy (6 Gy fractions) is expected to be very low and quite safe [16,17] As expected no cases of radiation retinopathy are observed until now

In conclusion, after a substantial period of follow-up (30 months), 7 out of 10 patients treated with a total dose of 24 Gy (6 Gy fractions) in the macular area, maintained a VA of 0 08 or better while, concerning the natural course data, 20% was expected This data, including the reduction in scar area after radiation treatment, suggest a beneficial effect of radiation therapy in subfoveal exudative age-related disease The overall conclusion during the meeting of the American Academy of Ophthalmology in October 1995 was that there is a strong theoretical basis for this therapy but that a definite answer has to come from long-term prospective randomized controlled trials In several centers over the world, including in the Netherlands,





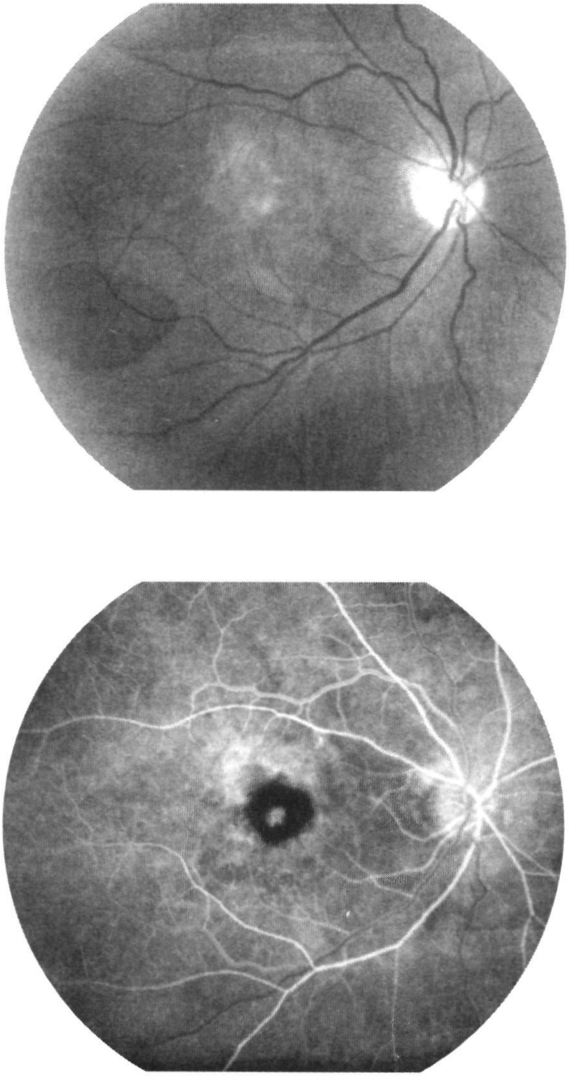
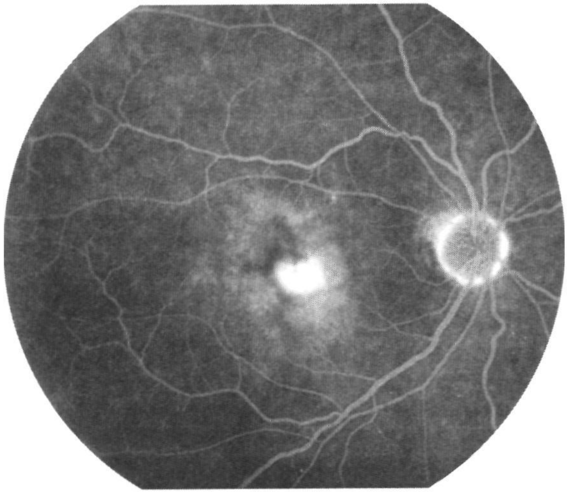


Figure 1. *Patient 1 with a classic type of CNV of the right eye and a VA of 0.3 at presentation before radiation treatment* **(left)**. *The VA was 0.2, 30 months after radiation treatment* (**right**). ***Top left,*** *red free picture at presentation.* ***Bottom left,*** *early phase at presentation.* ***Top right,*** *red free, 30 months after radiotherapy.* ***Bottom right,*** *early phase 30 months post-treatment.*



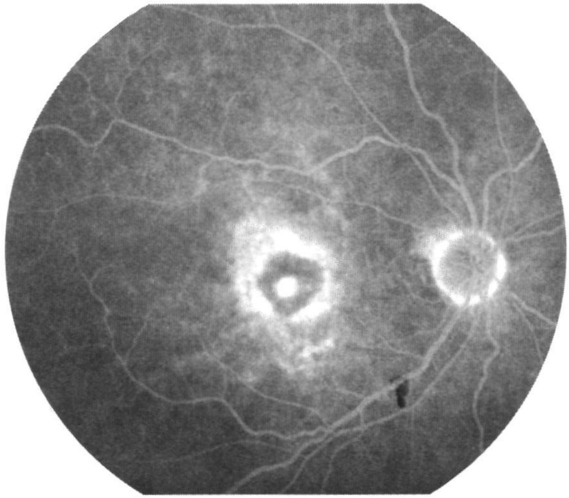
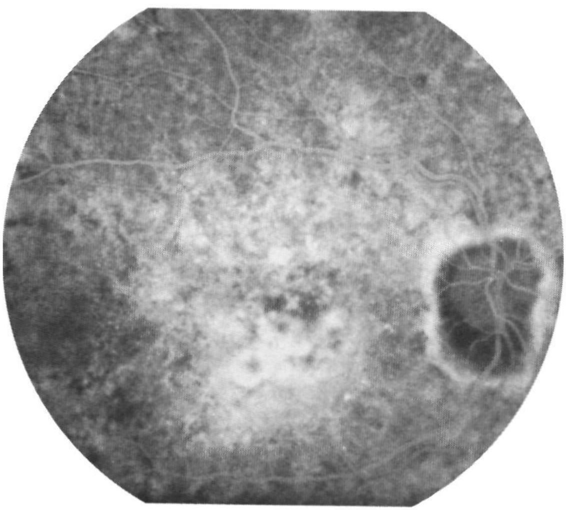


Figure 1. *Patient 1 with a classic CNV of the right eye and a VA of 0.3 at presentation and a VA of 0.2, 30 months after radiation treatment.* ***Left,*** *late phase at presentation.* ***Right,*** *late phase 30 months after radiation therapy. The late phase picture* ***(right)*** *shows a central SS of 1 DD and the late phase leakage is less compared with the pre-treatment angiogram of the same eye* ***(left)****.*



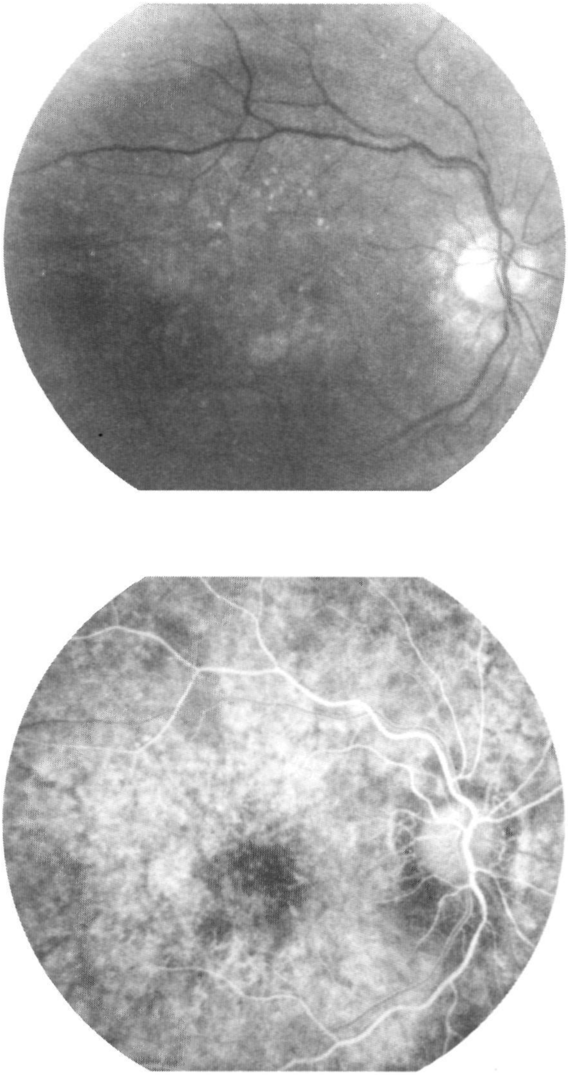


Figure 2. *Patient 4 with a CNV of the right eye and a VA of 0.25 at presentation before radiation treatment* ***(left)****. The VA was 0.1, 30 months after radiation treatment* ***(right)****.* ***Top left,*** *red free picture at presentation.* ***Bottom left,*** *early phase at presentation, with well-demarcated hyperfluorescence.* ***Top right,*** *red free, 30 months after radiotherapy.* ***Bottom right,*** *early phase post-treatment.*

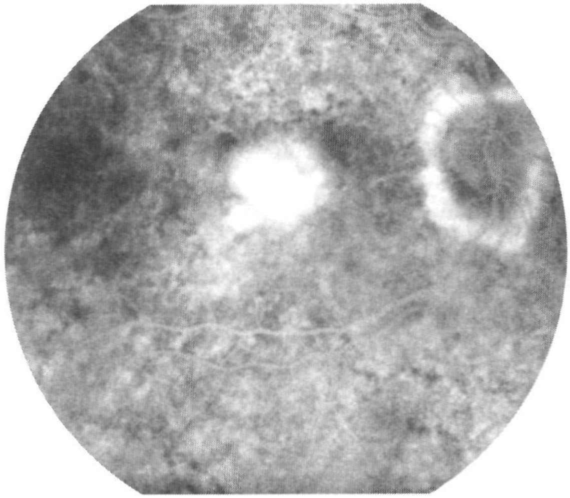


Figure 2. *Patient 4 with a CNV of the right eye and a VA of 0.25 at presentation and a VA of 0.1, 30 months after radiation therapy.* ***Left,*** *late phase at presentation.* ***Top right,*** *late phase 30 months after radiation therapy, with a central SS of 2 DD. The late phase leakage 30 months after radiation therapy (**top right**) is less compared with the late phase leakage at presentation (**left**).*

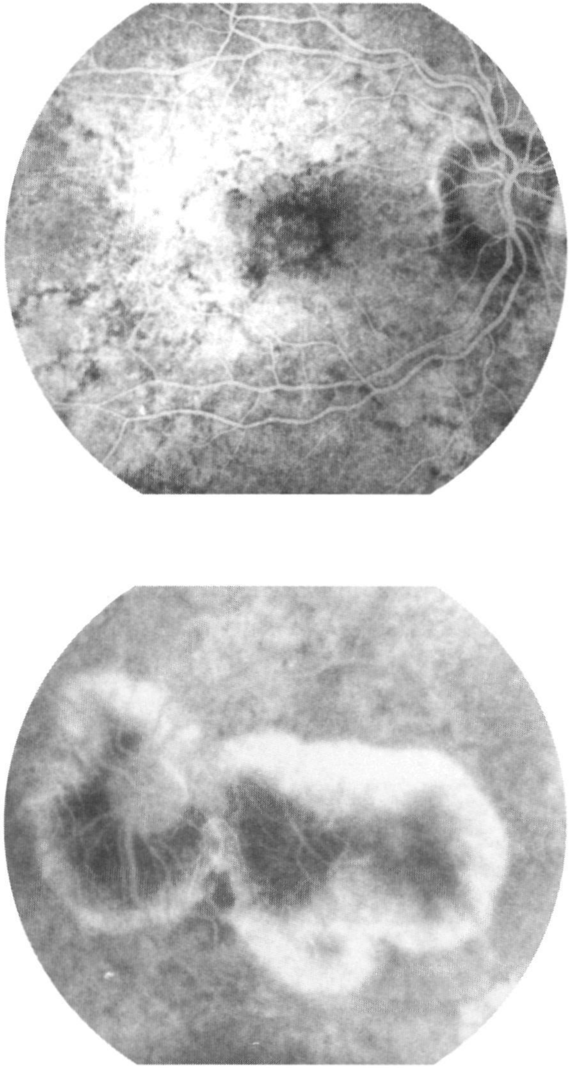


Figure 3. ***Bottom right,*** *late phase of the untreated left eye of patient 4 with disciform scarring and a stable SS of 6 DD after 30 months of follow-up. There is clearly a difference in scar size between the treated right eye 2 DD (**top right**) of patient 4 and the untreated left eye (**bottom right**). Although the patient had slight myopic correction in both eyes (S -2.0), she also had age-related peripapillary atrophy.*

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CHAPTER 7

A randomized controlled clinical trial on the efficacy of radiation therapy in the control of subfoveal choroidal neovascularisation in age-related macular degeneration. radiation versus observation.

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ABSTRACT

Background: The results of several pilot studies concerning radiation therapy for age-related subfoveal choroidal neovascularisation (CNV) have been published recently Although positive treatment results have been described, it is not known whether this therapy alters the natural course of eyes with neovascular age-related macular degeneration (AMD) A randomized controlled clinical trial was conducted in which radiation therapy was compared with observation in patients with subfoveal neovascular AMD

Methods: 74 patients with a recent drop in central vision due to subfoveal age-related CNV were randomized to either radiation treatment or observation Patients with either classic, occult or mixed type CNV were included Eyes in the treatment group received a radiation dose of 24 Gy in 4 fractions of 6 Gy Evaluation of data concerning visual acuity (VA) and fluorescein angiography occurred at 3, 6 and 12 months after inclusion

Results: At 12 months of follow-up 52 2 % of the observation group versus 32 0 % of the irradiation group had lost 3 or more lines (P=0 03 log rank test) More severe visual decline, 6 lines or more, was observed in 40 9 % of the observation versus 8 8 % in the irradiation group (P=0 002 using log rank test) At 12 months 39 6 % of the observation group and 20 0 % of the treatment group had lost their VA to less than 0 1 (P=0 08 log rank test) The size of the CNV membrane doubled in 25 2 % of eyes in the observation group versus 20 0 percent in the treatment group at 12 months (P=0 5 logrank test) Until now no side-effects have been observed

Conclusion: Preservation of visual acuity was significantly better in the treatment group compared with the control group at 12 months Nevertheless we noted a drop in central vision of 3 or more lines in a substantial part of the treatment group Radiation therapy does not prevent visual loss in all patients with age-related subfoveal CNV, and whether the treatment benefit at 12 months will last after longer follow-up has to be awaited

Introduction

Neovascular age-related macular degeneration (AMD) is responsible for severe visual loss in the elderly [14] Treatment of subfoveal choroidal neovascularisation (CNV) in AMD is a matter of great concern and debate The majority of CNV membranes have some degree of foveal involvement and are not eligible for laser photocoagulation therapy [1,6] Despite the Macular Photocoagulation Study Group (MPS) recommendations for laser photocoagulation in selected cases of age-related subfoveal CNV, most patients and ophthalmologists refrain from this treatment because it leads to immediate and permanent central visual loss [1,12,13] Alternative treatments are under investigation, including radiation treatment Since the first report in 1991 the follow-up of our pilot study has been updated [2,3,4] The Belfast study group noted that deterioration of visual acuity (VA) and scar size are less in irradiated eyes than in untreated eyes at 6 to 24 months of follow-up [10] Other groups confirmed these positive results [2,3,4,5,7] The natural course of CNV's depends on the type of CNV on angiography, and large variations between patients in these subtypes remain [6,9,11] A clinical trial was conducted to evaluate the effect of radiation therapy compared with no treatment for eyes with subfoveal CNV in AMD The primary objective of this study is to determine whether patients with age-related subfoveal CNV benefit from radiation therapy to maintain central vision

Materials and methods

The study protocol was approved by the institutional ethical committee Eligibility criteria are shown in table 1 The criteria include a history of recent drop in VA within 2 months caused by age-related subfoveal CNV and proven by fluorescein angiography (FA) The best-corrected VA should at least be more than 0 1 Snellen equivalent Patients were referred to the outpatient clinic of the University of Nijmegen by ophthalmologists throughout the Netherlands Patients who met the inclusion criteria were asked to participate in the trial and, after obtaining informed consent, patients were assigned randomly to either radiation treatment or observation

Table 1 Eligibility criteria

1	recent drop in central vision (within 2 months)
2	best-corrected Snellen visual acuity > 0 1
3	angiographically proven classic, occult or mixed type subfoveal CNV
4	clinical signs of ARM like drusen or pigment epithelial changes
5	age ≥ 55 years
6	informed consent
7	no previous laser photocoagulation in the macular area
8	no radiation treatment for ear, nose, throat or brain disease
9	no diabetes mellitus

Patients had a complete ophthalmic examination including best-corrected distance Snellen VA, Amsler grid testing, biomicroscopic slitlamp examination of the lens, 35°color fundus photographs and stereoscopic fluorescein angiography of the macular area and optic disc of both eyes VA was measured using a Snellen chart in a fixed examination unit under standard conditions A visual loss of 3 lines represents doubling of the minimum angle of resolution, eg, a change from 20/100 to 20/200, Snellen equivalent A history and a complete ophthalmic examination similar to the baseline examination, including angiography, was performed at 3, 6, and 12 months, after randomization Fluorescein angiography was performed using a standard protocol including early, mid-venous and late frames

Patients who were randomized to the radiation treatment group received a total dose of 24 Gy in 4 fractions of 6 Gy, given in an overall time of 3 weeks, in the macular area of the affected eye The dose was delivered by two 1 cm^2 16 MV photon beams using a lens-sparing technique [3] To reduce the lens dose the beams were directed 30° from the optical axis in the cranial/caudal direction and cross the eye axis in the macular area Only the macular area received the total dose, outside this area the dose decreased to less than 50 % of the total dose The lens received less than 30 % of the total dose The patients in the control group did not receive a sham radiation treatment

Patients with proven CNV on the FA were classified in three subgroups according to the MPS criteria patients with classic CNV, occult CNV, and mixed CNV, respectively [12,13] Classic CNV has an area of bright, well-demarcated hyperfluoresence in the early phase of the angiogram, with progressive dye leakage into the overlying subsensory retinal space in the late phase Occult CNV can be recognized by two angiographic patterns Type I is a fibrovascular pigment epithelial detachment with areas of irregular elevation of the retinal pigment epithelium (speckled hyperfluorescence) within one minute after dye injection, with persistent staining or leakage in the late phase after ten minutes Type II is late leakage of an undetermined source with areas of late phase leakage without early hyperfluorescence responsible for this leakage Mixed CNV is a CNV with classic and occult components The angiograms were independently graded by different investigators (JRV, CBH) 12 months after inclusion Discrepancies were openly adjudicated by the same two readers Discrepancies that could not be resolved were reviewed for final classification by a third ophthalmologist (GJB) The readers were blinded for the treatment status The features graded included 1 the type of CNV (classic, occult or mixed), 2 the size of the CNV lesion, determined by superimposing a transparent sheet with printed standard MPS disc area circles (1, 2, 3 5, 4, 6, 9 and 12) over the macular lesion [12,13]

The proportions of patients in the control and irradiation group losing 1 or more Snellen lines of vision and ending up with a VA < 0 1 were expected to be 70 % and 30 % respectively [3,4] A two-sided significance level of 0 05 and a power of 0 90 required 32 patients in both the treatment group and control group To anticipate a disability of follow-up and/or non-evaluable patients of 10 % in each group, 36 patients in both groups were necessary and 72 patients would be randomized into the trial

Differences in baseline characteristics were analyzed using t-test for comparing independent samples means Visual acuity scores and CNV lesion size were subgrouped in ordered variables Comparison of ordered variables was performed using Chi-square test for trend on one degree of freedom End points for VA decline was defined as 3 or more lines drop and 6 or more lines decline Other end points that were compared between treatment and observation group were VA less than 0 1 and doubling of CNV size Comparison of occurrence of end points in the treatment groups during follow-up was done with Kaplan-Meier curves and logrank tests

Results

Initially, 74 patients were included in the study Of these, one died and two stopped before the first control, one because of fear of malignancies due to the treatment In addition, one was excluded because of previously unnoted diabetes mellitus and two patients showed insufficient evidence for CNV on the angiogram later on As a result 68 patients, 36 treatment group and 32 observation group, completed at least three months follow-up Twelve months follow-up was obtained in 63 patients (Table 2) The baseline characteristics of both groups are shown in Table 3 Patients in the treatment group were slightly younger than controls Composition and area of lesion in the study eye, baseline visual acuity, presence and size of a neovascular lesion in the fellow eye and smoking behavior were similar

Visual decline of 3 or more lines was observed more frequently in the observation group than in the irradiation group (Figure 1) At 12 months, 52 2 percent of the observation group versus 32 0 percent of the irradiation group had lost 3 or more lines (P=0 03 log rank test) More severe visual decline, 6 or more lines, was observed in 40 9 percent of the observation versus 8 8 percent in the irradiation group (Figure 2, P = 0 002 using the log rank test) After 12 months, 39 6 percent of the observation group and 20 0 percent of the treatment group had lost visual acuity to levels less than 0 1 (P=0 08 log rank test) Additional analysis of subgroups of classic and occult or mixed type CNV suggests that there is a small effect in the classic CNV subgroup but a more pronounced beneficial effect in the occult and mixed type subgroup Differences, however, were not statistically significant The size of the CNV doubled during the 12 months in 25 2 percent of the observation group versus 20 0 percent in the treatment group This difference was not significant (P=0 5 logrank test)

Table 2 Number (percentage) of cases in the study

Follow-up	Study Group	
	Treatment	Observation
3 months	36 (100)	32 (100)
6 months	36 (100)	31 (96 9)
12 months	34 (94 4)	29 (90 6)

Table 3 Baseline characteristics of the study population by treatment group *

Characteristic	Study group				P[†]
	Treatment (N=36)		Observation (N=32)		
Mean age (SD)	73 1	(5 8)	76 1	(5 8)	0 07
Gender (% women)	20	(55 6)	18	(56 3)	0 96
Composition of lesion					
Classic	19	(52 8)	16	(50 0)	
Occult	8	(22 2)	8	(25 0)	0 96
Mixed	9	(25 0)	8	(25 0)	
Visual acuity					
≥ 0 1 - < 0 3	13	(36 1)	15	(46 9)	0 51
≥ 0 3	23	(63 9)	17	(53 1)	
Size of lesion, MPS grid					
≤ 1	13	(40 6)	15	(41 7)	
> 1 - ≤ 2	8	(25 0)	11	(30 6)	0 82
> 2 ≤ 4	10	(25 0)	8	(19 4)	
> 4	1	(9 4)	2	(8 3)	
Size AMD lesion fellow eye, MPS grid					
no lesion	19	(46 9)	15	(52 8)	
≤ 4	6	(25 0)	10	(11 1)	0 89
> 4	11	(28 1)	7	(36 1)	
Smoking					
Never	16	(44 4)	16	(50 0)	
Former	11	(30 6)	6	(18 8)	0 97
Current	9	(25 0)	10	(31 2)	

* Values are numbers with percentages in parentheses unless stated else [†]

P values from Chi-square statistics for unordered and ordered variables when applicable

Discussion

A visual decline of ≥ 3 lines was found more frequently in the observation group than in the treatment group at 12 months of follow-up This result became more pronounced concerning severe visual decline of ≥ 6 lines at 12 months Although these results are in favor of the treatment group, unfortunately still 32 0 % of treated eyes showed a visual decline of 3 or more lines at 12 months follow up vs 52 2 % in the observation group At 12 months follow-up 39 6 % of the observation group and 20 0 % of the treatment group had lost VA to levels less than 0 1 The results show an overall benefit of irradiation to prevent visual loss at 12 months follow up The differences appear to be mainly caused by the beneficial effect of irradiation of eyes with occult or mixed CNV's A small beneficial effect was seen in classic CNV only Irradiation had no significant effect on CNV size doubling but irradiated lesions tended to show less increase in size at 12 months follow-up

Concerning these findings we have to discuss some methodological points Differences in the course of the disease in the treatment groups could have occurred due to differences in baseline characteristics As can be seen from table 3, however, the baseline measurements were very similar and it is therefore unlikely that they are the cause of the differences in outcome The results are conform the expectations of the pilot study with respect to a beneficial effect of irradiation [4] Both treatment and observation group show a better course than expected however This is likely to be caused by the use of more strict inclusion criteria in this randomized trial Furthermore it suggests that the natural course of subfoveal CNV, with respect to the inclusion criteria, is less worse than anticipated Although the observers were blinded for treatment status, the patients were not This may have influenced the measurements of central vision But it is unlikely that this single blind situation may have caused the differences between treatment and observation group Differences in lesion size were less pronounced than could be expected from the differences in visual decline Partly this may have been due to the measurement of the lesions, e g growth of a lesion can occur within the limits of the baseline disc area On the other hand these results are based on objective criteria

Many uncontrolled pilot studies concerning radiation therapy for subfoveal neovascular AMD have been published with promising results but without definite proof of the efficacy of radiation treatment [2,3,4,5,7,10] After at least 30 months post-treatment with 24 Gy (6 Gy fractions) 5 out of 10 eyes with subfoveal exudative disease remained stable concerning VA and lesion size in our pilot study [3,4] The Belfast study group found a treatment benefit on central vision at 12, 18 and 24 months after irradiation and also a reduction of disciform scarring [10] In their study VA in treated eyes and VA in untreated eyes had worsened on average by 12 7 % and 52 7 % respectively at 12 months follow-up [10]

The main objective of irradiation is to induce inactivation of the CNV membrane with reducing the risk of subretinal fluid leakage or bleeding and subsequently leading to either stabilization of central vision and/or to a reduced scar size [3,5,7,10] There is no acute visual loss as does occur with laser treatment and until now no severe side-effects were encountered, although two patients experienced temporal conjunctival injection after treatment Maintenance of VA above a level of 0 1 Snellen acuity offers the patient the possibility to keep some visual function and to benefit from low-vision aids, most important in patients with exudative disease in both eyes Excluding eyes with a VA less than 0 125 offered the opportunity to determine a substantial drop in VA, important in the prevention of legal blindness Many patients presenting with subfoveal CNV, however, have Snellen VA of < 0 1 and will not benefit from treatment and subsequently, were not included in this trial

Recently data concerning 112 eyes in the natural history group during a trial with interferon became available [9] Loss of ≥ 3 lines at 1 year occurred in 58 % in the classic CNV group, and 35 % and 37 % in the occult and mixed CNV group respectively The difference in visual prognosis in case of classic CNV compared with occult and mixed CNV is important Plaque growth, reflecting the scar size in disc areas, doubled in 6 months in classic CNV and doubled in 12 months in occult and mixed CNV [9] We found that the size of the CNV membrane in all subgroups doubled in 27 6 % of the observation group versus 20 6 % in the treatment group, which was not significantly different

We used a total dose of 24 Gy with a fraction size of 6 Gy in 3 weeks only in the macular area (1 cm^2) This dose is biologically equivalent to 50 Gy in 25 daily fractions of 2 Gy [4] This radiation scheme gave the best results in our pilot study and offers the possibility to give a relatively high dose in the macular area without exceeding the tolerance levels of surrounding ocular tissues

Although this dose exceeds the total dose of 15 Gy (3 Gy fractions) used by the Belfast study group, our treatment volume is small compared with their technique of lateral irradiation [10] Radiation retinopathy and cataractogenesis was not observed as expected with a total dose in the macular area of 24 Gy and a 12 months period of follow-up

In conclusion our results show that there is a beneficial effect of radiation therapy for age-related subfoveal CNV at 12 months follow-up Preservation of central vision was significantly better in the treatment group vs the observation group Unfortunately, we noted a drop in central vision of 3 or more lines in a substantial part of treatment group Furthermore, we angiographically noted growth of neovascular membranes with progressive leakage in irradiated eyes, which at least indicate that not all treated neovascular membranes respond with growth arrest and reduced leakage Although the difference in favour of the radiation group concerning a drop in central vision of 3 or more lines at 12 months was significant, this result has to be taken with caution Irradiation does not prevent visual loss in all patients Whether the treatment effect will last for a longer period can not be answered yet Until longer follow-up is available we will be cautious propagating radiation therapy as a new treatment modality in recent age-related subfoveal neovascular membranes

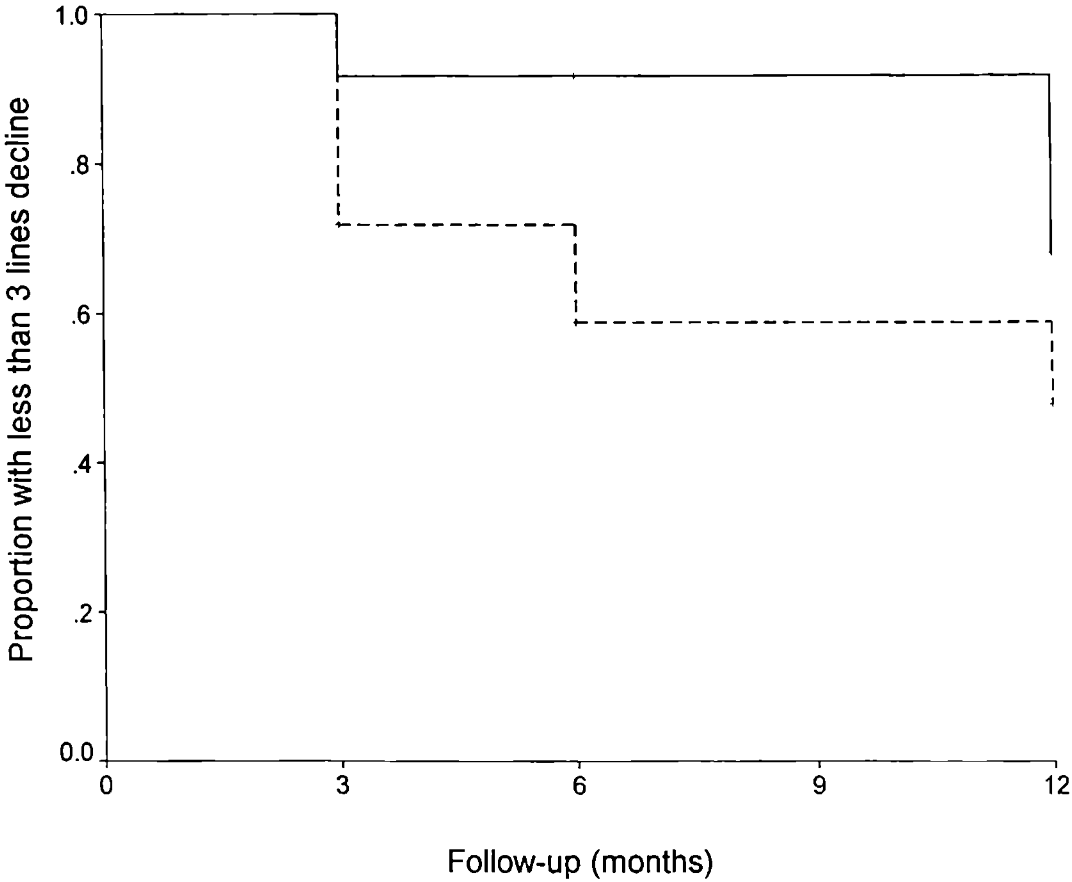
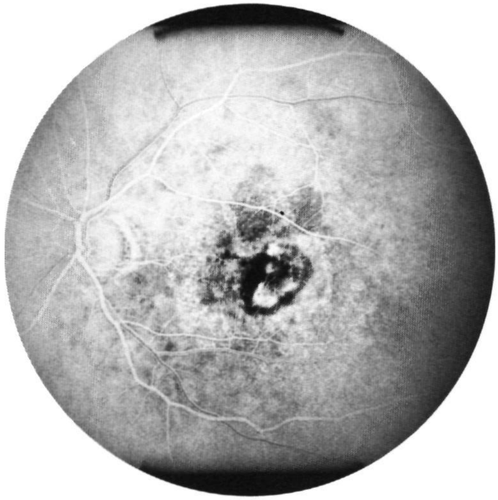
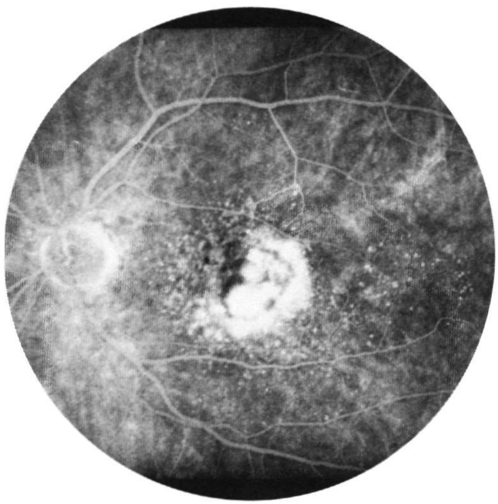


Figure 1. Kaplan-Meier curve for the proportion of eyes with decreases in visual acuity of 3 or more lines from baseline to each follow-up examination. Solid line indicates irradiated group (n=36), dashed line indicates observation group (n=32). P=0 03 using the log rank test.





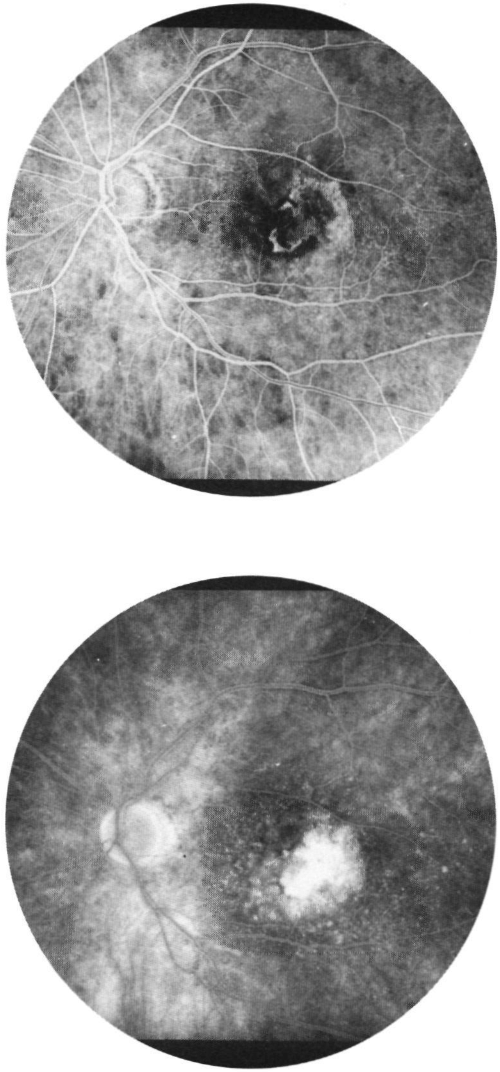


Figure 3. *Left eye of patient treated with radiotherapy in the randomized trial. An example of a stabilisation of a CNV membrane and visual acuity after treatment with radiotherapy.* ***Top left,*** *early phase of mixed type CNV at inclusion.* ***Bottom left,*** *late phase at inclusion.* ***Top right,*** *early phase 12 months after radiotherapy.* ***Bottom right,*** *late phase post-treatment. There is no increase in lesion size nor in late phase leakage at 12 months after radiotherapy.*

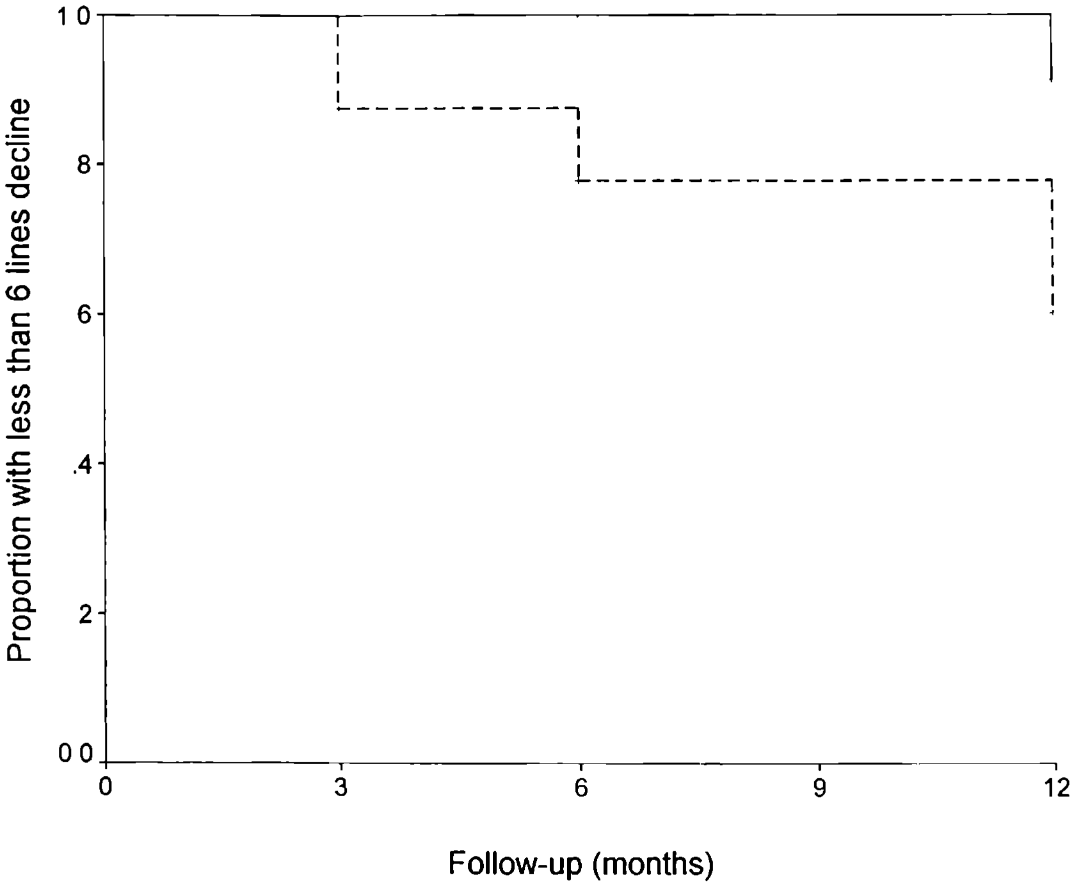


Figure 2. *Kaplan-Meier curve for the proportion of eyes with decreases in visual acuity of 6 or more lines from baseline to each follow-up examination. Solid line indicates irradiated group (n=36); dashed line indicates observation group (n=32). P=0 002 using the log rank test.*

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CHAPTER 8

GENERAL DISCUSSION

8.1 DISCUSSION AND CONCLUSIONS

Discussion

This thesis provides new and detailed information concerning radiotherapy for age-related subfoveal CNV During the last decades the knowledge about the detection, the natural course and laser photococoagulation treatment of CNV membranes increased substantially Despite new diagnostic procedures like ICG angiography, fluorescein angiography (FA) remains the diagnostic standard for detecting CNV membranes [3] What has changed is the description of CNV patterns on FA The MPS group propagated a classification based on FA changes associated with CNV that could lead to a standard definition of the various CNV membranes [1,2] This has the advantage that, for example, a classic CNV pattern is interpreted consistently Furthermore comparison of research results is more accurate when standard angiographic patterns are used The results of our pilot study were compared with natural history data as described by various research groups [4,5,6] These data were often but not always based on consistent descriptions of angiogram patterns

The various angiographic patterns of CNV membranes not only are of diagnostic help but they also have implications concerning the visual prognosis of the involved eye [7] We already knew that the majority of patients with subfoveal CNV were expected to develop severe visual loss [1,2] In comparison with occult and mixed CNV, classic membranes have a poor visual prognosis at 12 months [7] Beside the differences in natural course between CNV subgroups, differences between individuals make it difficult to predict the outcome of the VA for an individual eye Whether the two eyes of one person, with neovascular AMD in both, will behave in a same manner concerning visual acuity (VA) and disciform scar size is not sure

A pilot study was started partly based on the findings from basic research that considerable changes occur in human capillaries after a single radiation dose (8 7 Gy), leading to endothelial cell damage and capillary closure The patients treated with 24 Gy (6 Gy fractions) showed the best results after at least 12 months of follow-up However those treated with 12 Gy and 18 Gy also did better at 12 months compared with natural course studies The results of our pilot study indicated only CNV stabilisation but no CNV regression after irradiation, which differed from the findings of the Belfast study group [5] The reasons that can account for the different outcome between the Belfast pilot study and ours are: Firstly the inclusion criteria, with a distinction between the duration of several CNV membranes at presentation (> 2 months versus < 2 months), the baseline VA (some < 0.1 versus only > 0.1) and the presence of previous laser treatment (sometimes versus never); Secondly the radiation technique (lateral, 4 cm^2 versus frontal, 1 cm^2), the total dose (10-15 Gy versus 6-24 Gy) and the fraction size (2-3 Gy versus 6 Gy). Although in our pilot study we only noted CNV stabilisation without regression at 12 months, the observed scar size reduction compared with untreated fellow eyes at 30 months, supports the findings of the Belfast group. No side-effects were observed.

Our randomized study showed that irradiated eyes show significantly less visual loss at 12 months compared with no treatment [8]. This effect appears to be mainly caused by a beneficial effect on eyes with either occult or mixed types CNV's The effect of irradiation was expected to occur over a period of months resulting in a noticeable treatment effect between 6 and 12 months. In the randomized study, differences between the treatment and control group were already noticable at 3 months and persisted during follow-up [8]. Unexpectedly the untreated eyes showed less decline in VA at 12 months, when compared with natural history data published by various authors. Nevertheless more than 50 % of the observation group had lost 3 or more lines at 12 months follow-up. Concerning the lesion size we noted a slight difference in favour of irradiated eyes at 12 months. The relevance of these findings must be taken with caution because the development of the definite scar will take a longer period. We did not observe side-effects so far, however follow-up is still short.

Questions that remain to be answered in the following years are: 1. What will be the optimum treatment technique (teletherapy, brachytherapy, proton beam, stereotactic radiotherapy), the optimum total dose and dose per fraction ? 2. If regression or occlusion of CNV membranes occur, will it result in permanent stabilisation of VA and reduced scar formation ? 3. Do classic, occult and mixed CNV membranes respond in the same manner ? 4. Can we expect long term serious side-effects ?

The advantage of brachytherapy, proton beam and stereotactic therapy, compared with teletherapy, is the possibility to reduce the dose delivered to normal tissues. This may lead to less side-effects. Although we have been using a total dose (24 Gy, 6 Gy fractions) within the limits of serious side-effects, it is however not enough to induce and maintain CNV stabilisation or regression in all eyes Secondly it is known from our pilot study that a decrease in VA and increase in lesion size can occur after a period in which the VA and scar remained stable for at least 18 months, presuming a relapse or recurrence of CNV Thirdly the natural course of occult and mixed CNV is less deleterious than that of classic CNV It is speculative whether a difference in growth speed of a CNV, partly reflected in the natural history, can account for an increase in effect of radiotherapy Cataract, a possible side effect with current dose schemes, is a managable complication Hypothetically, the total dose leading to CNV regression in all eyes, will go beyond the limits of serious ocular side-effects, like radiation retinopathy Than the outcome may be that treatment with a higher dose only to the macular area will result in CNV regression in more patients However, the incidence of serious side effects can then be expected to increase

Conclusions

Considering the clinical significance of the results outlined in the randomized trial we conclude that, despite a significant treatment benefit at 12 months, radiation therapy with a total dose of 24 Gy (6 Gy fractions) applied with our technique will not prevent visual loss in all patients with recent age-related subfoveal CNV [8] Whether radiation therapy results in reduced scar size with stabilisation of central vision after longer follow-up has to be seen Radiotherapy does not cause an immediate visual loss, as seen after laser photocoagulation

Until we know the results after at least 2 years of follow-up, we have to be cautious recommending treatment with radiotherapy of patients with recent age-related subfoveal CNV Furthermore, before we draw definite conclusions about the efficacy of radiation therapy for this indication, we have to know the results of additional randomized trials using different radiation techniques and total doses If the treatment benefit lasts for two years or more we must take into account the reduced health care budgets and an aging population with growing demands and rising medical costs compared with the medical costs generated by those who are legally blind, when considering this potential therapy

It will be difficult to inhibit the effect of aging on the eye, nevertheless prevention of the development and growth of choroidal neovascularisation remains of great importance and will remain subject of further investigation and research

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8.2 Summary / Samenvatting

Age-related macular degeneration is the major cause of severe visual impairment in people over 55 years of age in Europe and the U S A The disease is located in the macular area, that part of the retina were central vision and color vision is located The neovascular stage of the disease leads to severe visual loss Many potential new therapies have been investigated, because there is no therapy which prevents growth of subretinal neovascularisation and at the same time does not destroy photoreceptors and subsequently central vision

The aim of this study is described in the first chapter The main question was whether irradiation of the macular area alters de course of eyes with age-related subfoveal neovascular disease

In chapter 2, the disease age related macular degeneration is described Most patients have the dry or atrophic type, and 10 20 % have the exudative type with the development of subretinal neovascularisation New capillaries, from the choroidal circulation broken through Bruch's membrane, proliferate subpigment epithelial and subretinal Beside a genetic predisposition, smoking and age are risk factors for age-related neovascularisation Concerning the pathogenesis of subretinal choroidal neovascularisation it has been proposed that drusen, changes in Bruch's membrane and hypoxia of the outer retina are interrelated factors leading to release of angiogenic stimuli

Fluorescein angiography is the most important value for the diagnosis of subfoveal neovascularisation According to the Macular Photocoagulation Study Group three types of fluorescein patterns can be described in case of subretinal choroidal neovascularisation e g classic, occult and mixed type

The natural course of eyes presenting with subfoveal choroidal neovascularistion has been described extensively and visual loss to levels < 0 1 occurred in 70 80 % of eyes within 18 months Although there is a small treatment benefit of laser photocoagulation for subfoveal neovascularisation, it is no standard treatment because only 13 % of eyes appear eligible and immediate loss of central vision occurs after laser treatment Many experimental therapies are being investigated including indocyanine green guided laser treatment, submacular surgery and retinal pigment epithelium transplantation

Chapter 3 describes the background of radiation therapy An overview of radiotherapy is presented including the influence of fraction size and total dose, and furthermore the differences between early and late responding tissue are discussed A review of the possible ocular side-effects of irradiation and the results of pilot studies concerning radiation therapy for subfoveal neovascularisation are given respectively

The results of our pilot study are given in chapter 4, 5 and 6 After treating groups of patients (n=10) with 8, 12, 18 and 24 Gy total dose in the macular area, we observed a positive treatment effect in the last 3 groups We decided to do longer follow-up in the 24 Gy (6 Gy fractions) group because of the best results concerning visual acuity and scar size compared with natural history data Severe side-effects, like radiation retinopathy, were not observed during the pilot study

Chapter 7 describes the results of a randomized clinical trial in patients with recent subfoveal age-related neovascular disease This trial, with a control group of untreated patients, resulted in better preservation of visual acuity in the treatment group at 12 months follow-up Although these results were conform the expectations after the pilot study, we conclude that radiation therapy does not prevent visual loss in all patients with age-related subfoveal neovascularisation, and that the natural course in untreated eyes at 12 months was better than expected Furthermore it has to be seen whether radiotherapy results in reduced scar size Questions that remain to be answered are 1 What will be the optimum treatment technique (teletherapy, brachytherapy, proton beam, stereotactic radiotherapy), the optimum total dose and dose per fraction ? 2 If CNV regression occurs, will it be a permanent effect ? 3 Do the various angiographic CNV types respond in a same manner ? 4 Do long term serious side-effects occur ?

Before drawing definite conclusions concerning radiotherapy for subfoveal CNV, results of other randomized trials with different techniques and dose schemes have to be awaited

Samenvatting

Leeftijdsgebonden (ouderdoms) macula degeneratie is de belangrijkste oorzaak van irreversibele daling van de visus (gezichtsscherpte) bij personen ouder dan 55 jaar in Noord-Amerika en West-Europa De aandoening betreft de macula lutea (gele vlek) in het centrum van de retina (het netvlies) Centraal in de macula lutea ligt de fovea centralis De fovea bevat fotoreceptoren, kegeltjes, verantwoordelijk voor de gezichtsscherpte en het kleurenzien Ouderdoms veranderingen worden in eerste instantie gekenmerkt door de aanwezigheid van drusen (afvalstoffen) en van hyper- en hypopigmentaties (veranderingen in de pigmentlaag) in de macula

Klinisch zijn er twee typen van leeftijdsgebonden macula degeneratie te onderscheiden te weten de atrofische of "droge" vorm, die bij 80-90 % van de patienten voorkomt, en de neovasculaire vorm, ook wel "natte" of exsudatieve vorm geheten Deze vorm ontstaat bij 10-20 % van de patienten en resulteert, in verloop van weken tot maanden, in een onherstelbare ernstige daling van de visus Als gevolg van een subretinale neovascularisatie (vaatnieuwvorming onder het netvlies) ontstaat er lekkage van vocht, bloed en lipoproteinen onder het netvlies van de macula Het eindstadium wordt gekenmerkt door een disciform (schijfvormig) litteken en een centraal scotoom (blinde vlek) Voor de neovasculaire vorm van leeftijdsgebonden macula degeneratie bestaat nog géén goede therapie, alhoewel in enkele geselecteerde gevallen de subfoveale neovascularisatie met laserstralen kan worden behandeld Deze foveale behandeling heeft echter altijd een directe afname van de nog aanwezige visus tot gevolg, maar geeft op den duur mogelijk wel een kleiner litteken en een kleiner centraal scotoom Experimentele behandelingen, met als doel de groei van de subretinale neovascularisatie te remmen zonder destructie van de retinale fotoreceptoren, zijn onderwerp van onderzoek in vele centra

In hoofdstuk 1 worden de doelstellingen van het onderzoek besproken Bij aanvang bestond de veronderstelling dat radiotherapie (bestraling) met een maximale dosis ter plaatse van de macula, de groei van subfoveale leeftijdsgebonden neovascularisaties kan remmen De belangrijkste beoordelings-criteria hierbij zijn het beloop van de visus en van het disciforme litteken

De voorstadia, de verschillende vormen en de mogelijke risico factoren van leeftijdsgebonden macula degeneratie worden in hoofdstuk 2 besproken De aanwezigheid van drusen en breukjes in de membraan van Bruch, de laag tussen de retina en de choriocapillaris (vaatvlies), en hypoxie (zuurstofgebrek) van de buitenste retina lagen zijn waarschijnlijk betrokken bij het ontstaan van angiogene (vaatgroei bevorderende) factoren verantwoordelijk voor het ontstaan van een subretinale neovascularisatie Als risicofactoren spelen naast leeftijd en genetische (erfelijke) aanleg waarschijnlijk ook omgevingsinvloeden zoals UV-licht, voedingsbestanddelen zoals vitamine C en E en carotenoiden en atherosclerose een rol Verder is voor de neovasculaire vorm aangetoond dat roken een zekere risico factor is

Bij het onderzoek van patienten is het klinisch van belang om met behulp van fluorescentie angiografie, de subfoveale neovascularisatie af te beelden Volgens recente indelingen kunnen zogenaamde "classsic, occult en mixed" typen van subretinale neovascularisaties fluografisch worden onderscheiden Het natuurlijk beloop van de typen subretinale neovascularisatie is verschillend Meestal groeit een subfoveale neovascularisatie zonder behandeling uit tot een groot disciform litteken in de maculastreek Over het algemeen is na 18 maanden in 70 tot 80 % van de ogen met een leeftijdsgebonden subfoveale neovascularisatie de visus gedaald tot minder dan 0 1 en is er een groot litteken ontstaan in de maculastreek

Hoofdstuk 3 begint met een bespreking van de achtergronden van radiotherapie Dan volgt een overzicht van het experimentele onderzoek betreffende effecten van bestraling van capillairen (haarvaten) Na bestraling nemen capillairen in aantal af en tonen minder lekkage Deze effecten van bestraling zouden ook bij de vaatnieuwvorming onder het netvlies kunnen optreden Verder worden de invloed van de totale bestralings-dosis, de fractie-dosis evenals de mogelijke korte en lange termijn bijwerkingen van bestraling besproken Met name de ooglens is zeer gevoelig Na bestraling kan cataract (staar) optreden Ook kan er een bestralingsretinopathie (netvliesschade door bestraling) ontstaan Tot slot volgt een overzicht van de resultaten van de verschillende internationale pilot onderzoeken In de meeste centra werden bemoedigende resultaten gevonden

De resultaten van het in Nijmegen verrichte pilot onderzoek, weergegeven in de hoofdstukken 4, 5 en 6 werden in artikelvorm gepubliceerd Samenvattend werden in de pilot studie groepen van patienten (n=10) bestraald met een totale dosis van respectievelijk 8 Gy, 12 Gy, 18 Gy en 24 Gy Na 1 jaar follow-up bleken de ogen bestraald met 12 Gy of meer, minder visus daling te tonen dan op grond van de literatuurstudies omtrent het natuurlijk beloop van de aandoening kon worden verwacht Omdat 8 van de 10 ogen in 24 Gy groep na 12 maanden een stabiele visus toonden werd besloten tot een langere follow up in deze groep Na 30 maanden hadden 5 ogen een stabiele visus en bestonden er aanwijzingen dat er in de andere 5 ogen, waarvan de visus verder gedaald was, een kleiner litteken was ontstaan dan in de onbehandelde tweede ogen met een disciform litteken van dezelfde patienten De littekens in deze tweede ogen waren ontstaan conform het natuurlijk beloop, zonder lasertherapie

Om de positieve resultaten van de pilot studie te objectiveren werd een protocol opgesteld voor een gerandomiseerde studie Hoofdstuk 7 is aan deze studie gewijd Na loting werden twee goed vergelijkbare groepen patienten met dezelfde afwijking en met dezelfde eigenschappen vervolgd Ogen met een recente leeftijdsgebonden subfoveale neovascularisatie kregen, na randomisatie, of radiotherapie met 24 Gy (6 Gy fracties) of géén behandeling (controle groep) Na 12 maanden follow-up waren er in de met radiotherapie behandelde groep significant (statistisch bewezen) minder ogen met 3 of meer regels visus verlies dan in de controle groep In de met radiotherapie behandelde groep toonden echter 32 % van de ogen 3 of meer regels visus verlies na 1 jaar Radiotherapie met 24 Gy en fracties van 6 Gy voorkomt dus niet bij alle ogen met een recente subfoveale neovascularisatie een verdere visusdaling

Alvorens tot definitieve conclusies te komen moeten de resultaten van dit onderzoek na 2 jaar follow-up bekend zijn Met name de effecten van radiotherapie op het behoud van de visus en de mogelijke effecten op de litteken stabilisatie, ten opzichte van onbehandelde ogen, zullen dan waarschijnlijk duidelijker zijn Nadat ook de resultaten van de buitenlandse gerandomiseerde studies met andere bestralingstechnieken en bestralingsdoses bekend zijn, wordt het mogelijk om de plaats van radiotherapie in de behandeling van leeftijdsgebonden subfoveale neovascularisaties nauwkeuriger te bepalen

Nawoord

De beschreven studies zijn in samenwerking tussen de afdeling Oogheelkunde (hoofd Prof dr A F Deutman) en de afdeling Radiotherapie (hoofd Prof dr W A J van Daal) van het Academisch Ziekenhuis Nijmegen tot stand gekomen Velen ben ik dankbaar voor hun bijdrage, enkelen wil ik met name noemen Professor Deutman stimuleerde mij tot het schrijven van dit proefschrift, ik dank hem voor de mogelijkheid die hij mij geboden heeft om oogarts te worden Verder zijn onderstaande personen betrokken geweest bij de studie en verdienen mijn woord van dank

Richard van der Maazen, heeft als radiotherapeut de meeste patienten behandeld Hij heeft ook in belangrijke mate bijgedragen aan het hoofdstuk over radiotherapie

Carel Hoyng heeft, in samenwerking met vele Nijmeegse assistenten, een groot deel van de patienten geincludeerd tijdens de trial en heeft geholpen bij de analyse van de angiogrammen De geanimeerde gesprekken over het onderzoek en andere zaken waren altijd weer een punt van herkenning

Hans Vingerling heeft naast zijn hulp bij de analyse van de angiogrammen gezorgd voor een betrouwbare epidemiologische en statistische onderbouwing van de gerandomiseerde studie Onze discussies, ook over de interpretatie van de onderzoeksresultaten, blijven zeer boeiend

Albert Aandekerk, Evert-Jan Steenbergen en de andere medewerkers van de fotografie afdeling voor het maken van de vele macula angiogrammen en voor het dia- en fotomateriaal

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Tenslotte, lieve Saskia, dank voor alles en speciaal voor Gijs

Curriculum vitae

De auteur van dit proefschrift werd op 13 januari 1959 geboren te Den Haag In 1977 behaalde hij het diploma Atheneum B aan het Rijnlands Lyceum te Wassenaar Na een jaar Geneeskunde in Gent (Belgie) en een jaar Farmacie werd in 1979 begonnen met de studie Geneeskunde aan de Rijksuniversiteit Leiden, alwaar het arts examen in het voorjaar van 1987 werd behaald Van 1987 tot 1989 heeft hij onder andere als AGNIO Oogheelkunde gewerkt in het Leyenburg Ziekenhuis te Den Haag Van 1 oktober 1989 tot 1 oktober 1993 volgde de opleiding tot oogarts aan het Instituut voor Oogheelkunde van het Academisch Ziekenhuis Nijmegen (opleider Prof dr A F Deutman) Daarna bleef hij daar als oogarts tot september 1995 werkzaam Sindsdien is hij als oogarts verbonden aan het Academisch Ziekenhuis Rotterdam (Dijkzigt), met als aandachtsgebieden retina en chirurgie van voor- en achtersegment

Meer en meer leiden wij babbelaars op, mensen die anderen aansturen in plaats van zelf iets te kunnen. Alsof vakkennis en leiding geven niet samen kunnen gaan.

(P. Borst)

STELLINGEN

behorende bij het proefschrift

Radiotherapy for subfoveal choroidal neovascularisation in age-related macular degeneration

G.J. Bergink

1 Het natuurlijk beloop van ogen met een leeftijdsgebonden (ouderdoms) subfoveale neovascularisatie gaat in meer dan 50 % van de ogen gepaard met een visusdaling van 3 of meer regels in het eerste jaar

2 In de groep met radiotherapie (24 Gy, 6 Gy fracties) behandelde ogen met een leeftijdsgebonden (ouderdoms) subfoveale neovascularisatie is, na één jaar, bij minder ogen een ernstige visusdaling opgetreden dan in de onbehandelde controle groep

3 Radiotherapie is niet de oplossing voor het probleem van de neovasculaire vorm van leeftijdsgebonden (ouderdoms) macula degeneratie

4 Naast deelspecialisten, blijven er all-round oogartsen/chirurgen nodig

5 Patienten die op een wachtlijst staan voor een poliafspraak of oogoperatie kunnen gedurende de wachttijd niet genieten van de door hun zorgverzekeraar gesponsorde voetbalclub of sportevenement

7 De vaak gehoorde uitspraak bij een second opinion "twee weten meer dan één", suggereert ten onrechte dat de som der kennis van twee artsen (m/v) over een probleem altijd groter is dan die van ieder afzonderlijk

8 De aandacht voor de scherpte van de schaats is vaak onevenredig groot vergeleken met die voor de bolling

9 Het belang van een goed evenwicht tussen in- en ontspanning blijkt uit de opmerking dat de Tour de France in bed gewonnen wordt

10 Als het carrièreperspectief voor artsen alleen gaat bestaan uit de overstap naar het management, ziet de toekomst voor de patient er zorgelijk uit

11 Het poldermodel is géén mooi Hollands (ver)gezicht en de wet BIG géén beperking van het aantal varkens, echter beiden zijn een uiting van voortschrijdende bureaucratie

Nijmegen, 6 maart 1998